博士論文

論文題目　Development of Functional Group Tolerated Cu(I)-Catalyzed Asymmetric C-C Bond Forming Reactions

(保護基フリー合成を指向した不斉銅触媒による
C-C 結合形成反応の開発)

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Contents

Abbreviations

Ac	acetyl
aq.	aqueous solution
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl protecting group
BPE	1,2-bis(2,5-diphenylphospholano)ethane
dr	diastereomeric ratio
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DTBM-SEGPHOS	5,5'-bis[3,5-(di-*tert*-butyl-4-methoxyphenyl)phosphino] 4,4'-bi-1,3-benzodioxole
DMPU	*N*,*N'*-dimethyl-propyleneurea
dppm	1,1-bis(diphenylphosphino)methane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
Et	ethyl
eq	equivalent
ESI-MS	electrospray ionization mass spectrometry
GlcNAc	*N*-acetyl-D-glucosamine
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectroscopy
IPA	isopropyl alcohol
i-Pr	*iso*-propyl
KDN	2-keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid
LRMS	low-resolution mass spectroscopy
M	molar
ManNac	*N*-acetyl-D-mannosamine
MTBE	methyl *tert*-butyl ether
Mes	mesityl
Me	methyl
MS	molecular sieve
NBS	*N*-Bromosuccinimide
ND	not determined
Neu5Ac	*N*-Acetylneuraminic acid
Neu5Gc	*N*-glycolylneuraminic acid
NMP	*N*-methyl-2-pyrrolidone

NMR	nuclear magnetic resonance
N	normal
nOe	nuclear Overhauser effect
n-Bu	*normal*-butyl
OTf	trifluoromethanesulfonate
Ph	phenyl
quant.	quantitative
R	substituent
rt	room temperature
t-Bu	*tert*-butyl
Tf	Trifluoromethanesulfonate
TFA	trifluoroacetic acid
TMS	tri-methylsilyl
Tr	triphenylmethyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
temp.	temperature

1. Recent progress on functional group tolerated Cu(I)-catalyzed asymmetric C-C bond forming reactions

1.1 Introduction

Asymmetric catalysis is indispensable for the synthesis of a plethora of enantiomerically-enriched compounds [1] . Taking current high demands for environmentally benign molecular synthesis into account, asymmetric catalysis bestowed with high atom-[2] and step-economy[3] is desirable, especially for industrial-scale applications.

Protecting groups have been widely used in synthetic organic chemistry. Despite the merits for secured molecular conversion, the atom- and step-economy of the overall molecular synthesis decreases. Thus, minimizing the use of protecting groups is critically important toward realizing efficient molecular synthesis. Although nucleophilic addition of organometallic reagents to carbonyl compounds has played a pivotal role in organic synthesis since the original work of Butlerov[4] and Grignard,[5] such transformation are facing formidable challenge in the presence of unprotected protic functional groups. Since it is generally difficult to separate the nucleophilicity and Brønsted basicity of polar organometallic alkylating reagents, protonolysis of the reactive species by protic functional groups can be competitive to the desired C–C bond-formation. [6] From the viewpoint of green chemistry, the development of catalytic asymmetric C–C bond-forming reactions without protecting groups [7] is of great importance.

1.2 Hard anion-conjugated soft metal catalysis (HASM)

Using the hard-soft mismatched characteristics of hard anion (X)-conjugated soft Cu(I) salts (CuX: X = F, OR), our group has identified general methods to catalytically generate a variety of reactive carbon nucleophiles for asymmetric addition to carbonyl groups and imines (**Figure 1.2.1**)[8]. We named the basic concept underlying these reactions as hard anion-conjugated soft metal catalysis (HASM). The soft-soft Lewis acid-Lewis base interaction between Cu(I) and the π-electrons of a carbon *pre*-nucleophile (*C*-Nuc–M) polarizes the C–M bond of the *pre*-nucleophile, thus promoting the transfer of the hard anion X of the catalyst to the hard M of the *pre*-nucleophile, which are interacting with each other with a hard-hard interaction (**Figure 1.2.1**, **1**). The soft carbon nucleophile (*C*-Nuc) is then transferred to the soft Cu(I), generating a Cu(I)-conjugated carbon nucleophile (Cu–*C*-Nuc) and MX, containing soft-soft and hard-hard interactions, respectively. In other words, by taking advantage of the soft-hard mismatched characteristics of catalyst CuX, the nucleophile activation process becomes thermodynamically favorable.

Introduction of chiral phosphine ligands to CuX catalysts makes various catalytic asymmetric reactions possible. Using this basic concept, our group has achieved catalytic asymmetric addition reactions of allylsilicones [9], allylboronates [10], alkenylsilicones[11], alkenylboronates[12], arylsilicones[9], arylboronates[10,13] and ketene silyl acetals[14] activated through transmetalation, ester enolates generated through conjugate reduction [15] or alkylation [16] of α,β-unsaturated esters, nitriles activated though decarboxylation from cyanocarboxylic acids[17] or deprotonation[18], and alkynyl groups activated through deprotonation[19]. These results demonstrate that HASM can be a general concept for catalytic activation of nucleophiles from stable molecules. In the following sections, I describe that chiral Cu(I)-conjugated carbon nucleophiles, generated by the HASM concept, act as soft nucleophiles, and chemoselectively react with carbon electrophiles, even in the presence of protic functional groups.

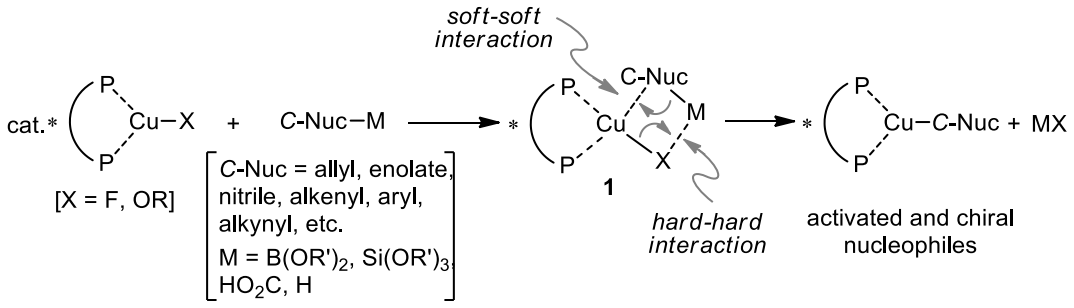


Figure 1.2.1. General concept for nucleophile activation through hard anion-conjugated soft metal catalysis (HASM)

1.3 Copper(I)-catalyzed chemoselective and asymmetric C-C bond-forming reactions in the presence of protic functional groups

1.3.1 Copper(I)-catalyzed asymmetric addition of enolates and their equivalents

Shibasaki and Kanai developed a catalytic enantioselective nitrile aldol reaction using CuO*t*-Bu–DTBM-SEGPHOS complex as a catalyst (**Figure 1.3.1.1**)[17, 20]. The C–C bond-formation proceeds in the presence of alcohol products, because the active nucleophile generation is reversible under the reaction conditions, and also soft copper ketene imide prefers the attack to the soft aldehyde carbon rather than the attack to the hard alcohol proton at least to some extent.

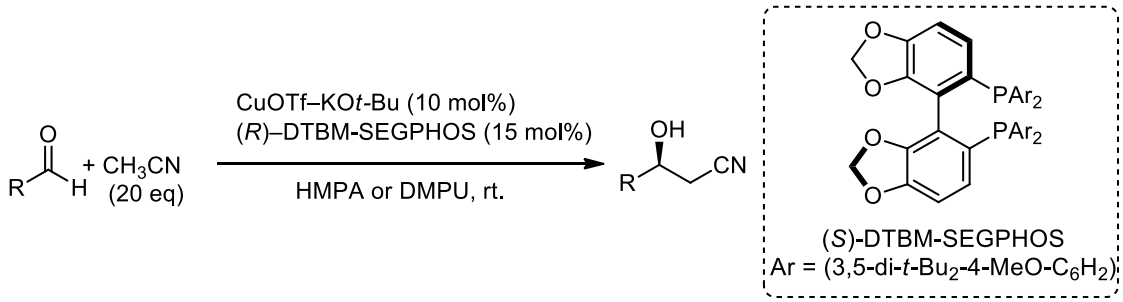


Figure 1.3.1.1. Copper(I)-catalyzed asymmetric addition of acetonitrile to aldehydes

On the basis of this finding, Shibasaki group developed a series of asymmetric reactions using soft copper(I) Brønsted base catalysts and a wide variety of *pro*-nucleophiles (thioamides[21], isocyanide[22], unsaturated butyrolactones[23], nitroalkanes[24], allyl cyanide[25], and α-trifluoromethyl acetamide[26]) *via* proton transfer strategy (**Figure 1.3.1.2**). The protonic functional groups, which were generated after the protonation of corresponding products, did not influence the catalyst turn over.

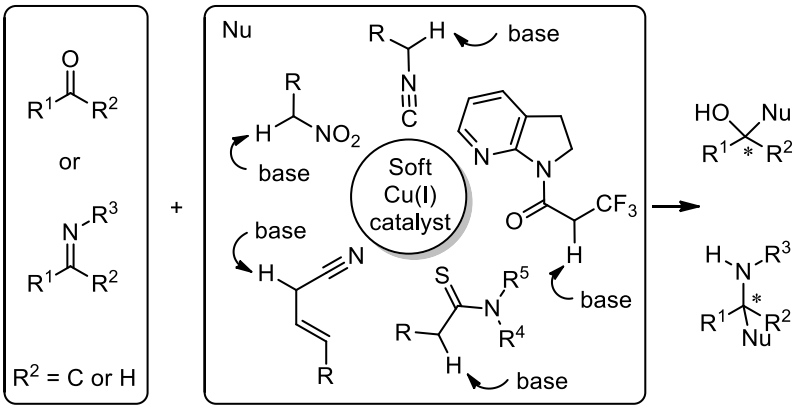


Figure 1.3.1.2. Representative examples for Cu(I)-catalyzed asymmetric addition reactions through nucleophile generation via deprotonation, affording products containing protic functional groups

Dihydropyranones **3** are synthetically useful chiral building blocks for drug lead compounds. Kanai group reported a catalytic asymmetric synthesis of **3** from ynones **2** and aldehydes through sequential copper(I)-catalyzed asymmetric direct aldol reaction and silver(I)-catalyzed oxy-Michael reaction (**Figure 1.3.1.3)**.[27] The addition of trifluoroethanol in a (sub)stoichiometric amount (40–200 mol%) is crucial for high yield in the aldol reaction step. The catalytic asymmetric C–C bond-formation in the presence of a relatively acidic alcohol additive (pK_a of trifluoroethanol = 23.5 in DMSO, cf. pK_a of α-C–H of acetophenone = 24.7 in DMSO) is noteworthy, and this is again due both to reversible enolate formation under the reaction conditions, as well as the nature of soft Cu(I) enolates. The additive stabilizes the aldol products, probably by reducing the basicity of the reaction media; use of 40 mol% additive is enough for the reactions with aliphatic aldehydes (R^1 = aliphatic groups), affording relatively stable aldol products, while for aromatic aldehydes (R^1 = aromatic groups) the aldol products are less stable and a superstoichiometric amount of additive is necessary for a high product yield. After the asymmetric aldol reaction, AgOTf-catalyzed oxy-Michael reaction produced enantiomerically-enriched dihydropyranones **3**.

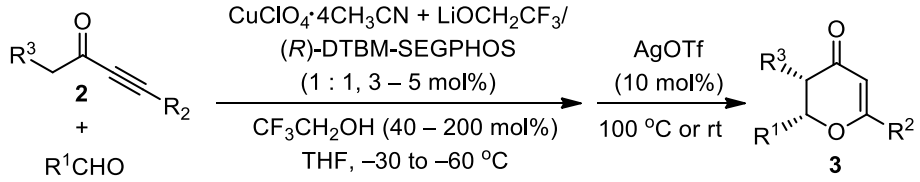


Figure 1.3.1.3. Catalytic asymmetric dihydropyranone synthesis through Cu(I)-catalyzed asymmetric aldol reaction and subsequent Ag(I)-catalyzed oxy-Michael reaction.

Among protic species, water is the most problematic for Cu(I)-conjugated Brϕnsted base catalysts due to the instability of Cu(I)OH. Cu(I)OH is considered to decompose into insoluble and polymeric Cu_2O by dehydration[28]. In 2012, our group developed an enantioselective condensation between ketones and cyclic hemiaminals **4** using

copper(I) catalyst (**Figure 1.3.1.4**)[29]. Products **5** are important intermediates in biosynthesis of various pyrrolidine and piperidine alkaloids, and thus are versatile chiral building blocks in alkaloid synthesis. Despite their synthetic versatility, however, there was no practical catalytic enantioselective synthesis of **5** prior to our report. The Cu(I)-catalyzed enantioselective reaction is of broad substrate generality, covering aliphatic and aromatic ketones for the donor substrates and five-, six- and seven-membered cyclic hemiaminals for the acceptor substrates. Although water is generated during the reaction progress, the addition of catalytic amounts of water at the beginning slightly improved the enantioselectivity.

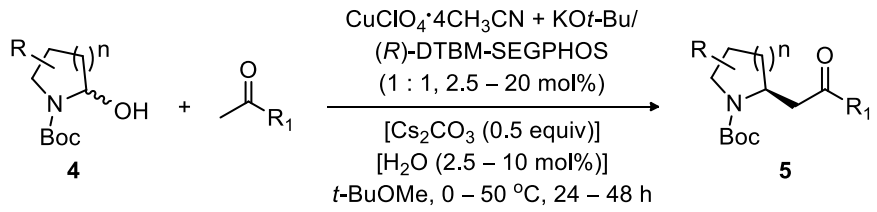


Figure 1.3.1.4. Copper(I)-catalyzed enantioselective condensation of ketones and cyclic hemiaminals

The catalytic cycle is proposed as shown in **Figure 1.3.1.5** The reaction process includes: (1) base-promoted facilitation of the equilibrium between hemiaminal **4** and aldehyde **6**; (2) chemoselective deprotonation of donor ketones by the Cu(I) alkoxide catalyst to generate Cu(I) enolate **7**, likely due to the large relative concentration difference between donor ketones and aldehyde **6**; (3) aldol reaction between enolate **7** and **6** to produce **8**; (4) Cu(I) alkoxide-catalyzed dehydration of **8** to generate enone **9**; and (5) Cu(I) alkoxide-catalyzed enantioselective intramolecular aza-Michael addition to give enantiomerically-enriched product **5**. The Cu(I) catalyst plays multiple roles in this catalytic cycle. Keys to the success of this reaction are again the reversible enolate formation and the nature of soft copper(I) enolates acting as a carbon nucleophile, even in the presence of the hard hydroxy groups of the substrates and water added or generated in the reaction.

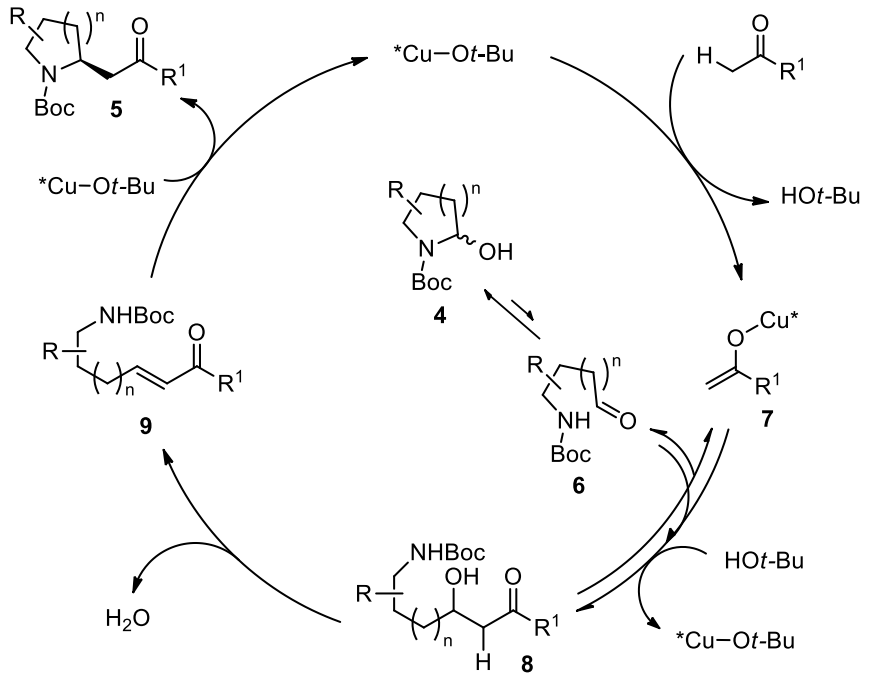


Figure 1.3.1.5. Proposed catalytic cycle for copper(I)-catalyzed enantioselective condensation of ketones and cyclic hemiaminals

The Cu(I) catalyst was further applied to the anomeric aminoalkynylation of unprotected sugars (**Figure 1.3.1.6**)[30]. Although the diastereoselectivity was not governed by catalyst,[31] the result is noteworthy because it demonstrates that the soft copper-conjugated carbon nucleophiles (copper alkynides) can react with carbon electrophiles (iminium species generated from sugars and diallylamine) containing multiple hydroxy groups.

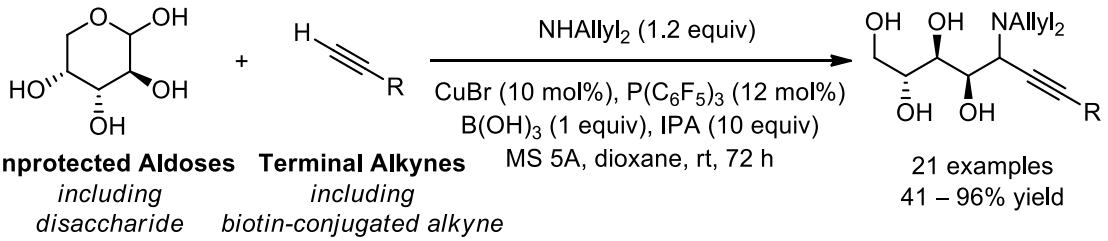


Figure 1.3.1.6. Copper-catalyzed anomeric aminoalkynylation of unprotected aldoses

1.3.2 Copper(I)-catalyzed nucleocupration of allenes followed by asymmetric addition

In the examples mentioned above, the generation of reactive Cu(I)-conjugated carbon nucleophiles through deprotonation of *pre*-nucleophiles is a reversible process. Although the characteristics of the Cu(I)-conjugated soft nucleophiles should play an important role in chemoselective C–C bond-formations compared to protonation, it is not critical for the reactions described in section 1.3.1. In the case when generation of Cu(I)-conjugated carbon nucleophiles is irreversible, however, extremely high chemoselectivity is an essential requirement. To challenge this issue, our group studied an intramolecular oxycupration approach[32] for the catalytic generation of organocopper species from allenyl alcohol **10**. The thus generated organocopper species were subsequently applied to asymmetric addition to aldehydes and a ketone in a one-pot procedure (**Figure 1.3.2.1**)[33]. Key for the success of this reaction relies on the chemoselective and enantioselective addition of the intermediate organocopper species to carbonyl compounds in the presence of stoichiometric hydroxy groups of the starting allenyl alcohols. The product isochromenes **11** are useful synthetic intermediates for many drug lead compounds.

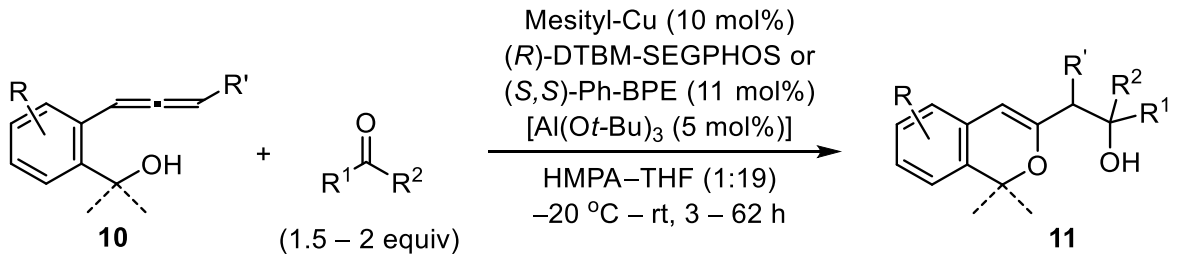


Figure 1.3.2.1. Consecutive Cu(I)-catalyzed oxycupration followed by asymmetric addition of carbonyl compounds for isochromene synthesis

This strategy was extended to the synthesis of enantiomerically-enriched 2-(2-hydroxyethyl)indole derivatives starting from allenyl anilides[34] through a consecutive amidocupration, followed by enantioselective addition of the resulting nucleophilic organocopper species to aldehydes and ketones (**Figure 1.3.2.2**). The reaction proceeded in the presence of protonic amide functional group in starting material as well as the free hydroxyl group in product.

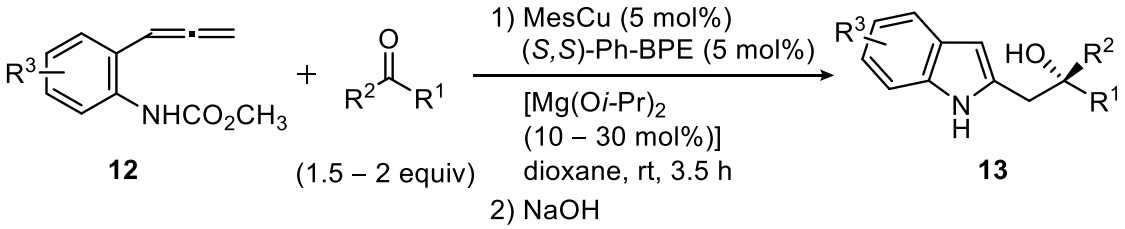


Figure 1.3.2.2. Consecutive Cu(I)-catalyzed amidocupration followed by asymmetric addition of carbonyl compounds for indole synthesis

1.4 Conclusion and outlook

Recent progress in asymmetric addition reactions of soft Cu(I)-conjugated carbon nucleophiles in the presence of protic functional groups was described, mainly focusing on chemoselectivity. Protic functional groups of amides, hydroxy groups and even H_2O are compatible in the copper catalyzed asymmetric reactions. Such characteristics of copper catalyzed asymmetric C–C bond-forming reactions will give rise to various opportunities for the application to late-stage structural optimization of drug lead compounds and protecting group-minimized synthesis of multifunctional complex molecules. Representative challenges in this field are; (1) improving the external ligand-controlled enantioselectivity and diastereoselectivity, especially when the substrate contains multiple chiral centers with polar functional groups, such as polysaccharides and peptides, and (2) developing novel catalytic generation methods for copper nucleophiles, enabling high atom- and step-economy.

2. An expeditious synthesis of sialic acid derivative by copper(I)-catalyzed stereodivergent propargylation of unprotected aldoses

2.1 Introduction

Sialic acids, which comprise a polyfunctionalized 9-carbon α-keto carboxylic acid skeleton, are present at the non-reducing end of glycan chains of various glycoproteins and glycolipids. *N*-Acetylneuraminic acid (Neu5Ac), *N*-glycolylneuraminic acid (Neu5Gc), and 2-keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) are representative examples of the more than 50 naturally occurring sialic acids (**Figure 2.1.1**).[35] Due to their remarkable structural diversity and prevalent distribution on the outer surfaces of cells, many extra-cellular proteins such as siglecs,[36] selectins,[37] and sialidases,[38] use sialic acids as specific recognition markers. The sialic acids-protein interactions are of special interest in sialobiology and drug discovery, since they regulate a variety of fundamental biologic events, including cell-cell recognition,[39] neurobiologic functions,[40] cancer metastasis,[41] and viral infections.[42] In the quest for selective inhibitors of these interactions,[43] a facile access to a wide variety of sialic acid derivatives is pivotal. Sialic acid derivatives containing unnatural stereochemistry are potential inhibitors of sialic acid-recognizing proteins.[44]

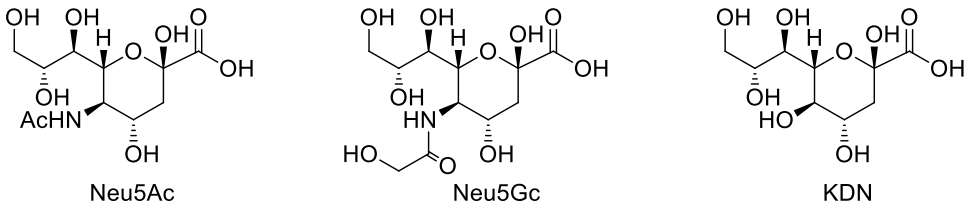


Figure 2.1.1. Representative sialic acids

In this context, several elegant sialic acid syntheses from readily available carbohydrates have been developed. In 1993, Whitesides group reported an indium-mediated allylations of unprotected carbohydrates using *N*-acetyl-D-mannosamine as

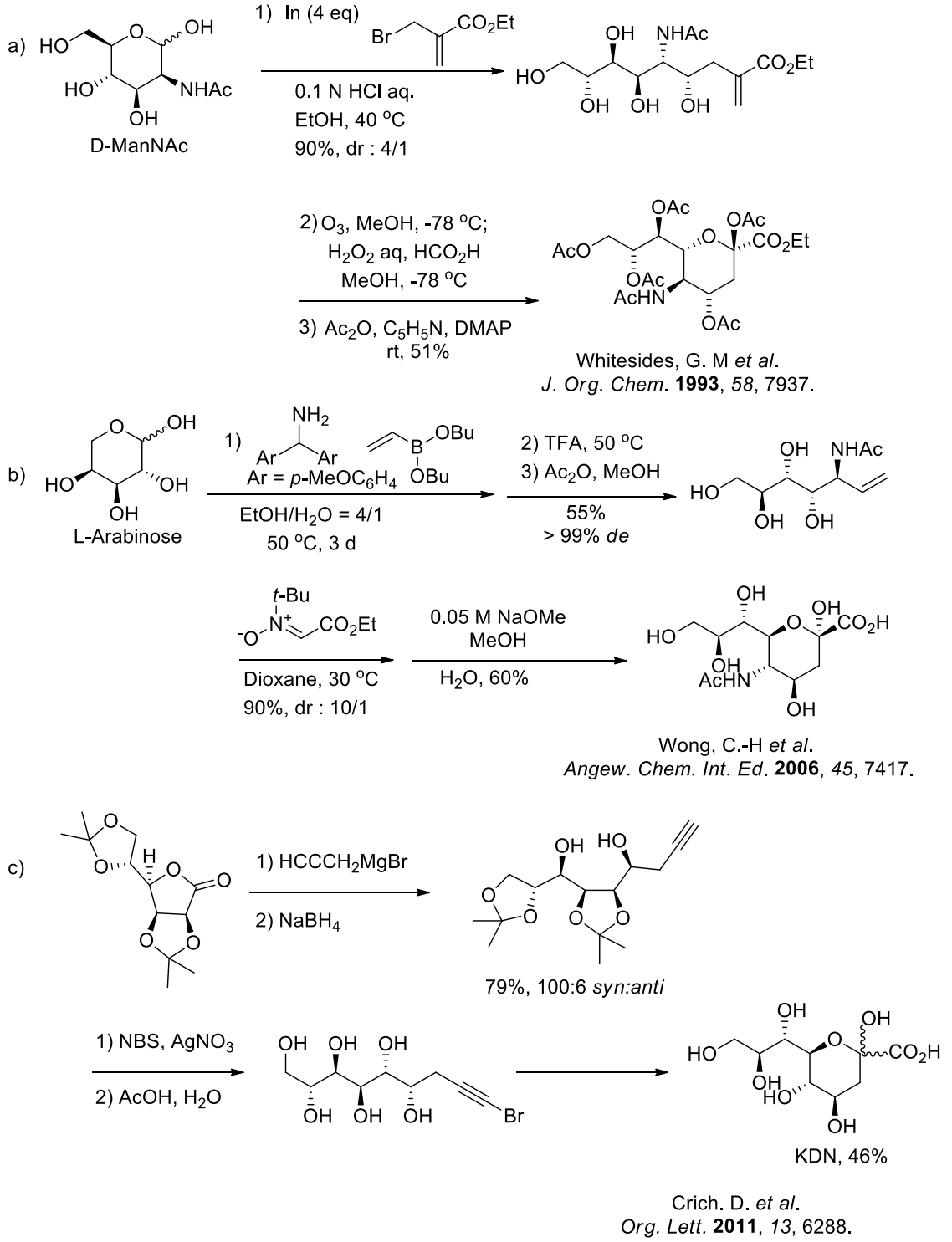
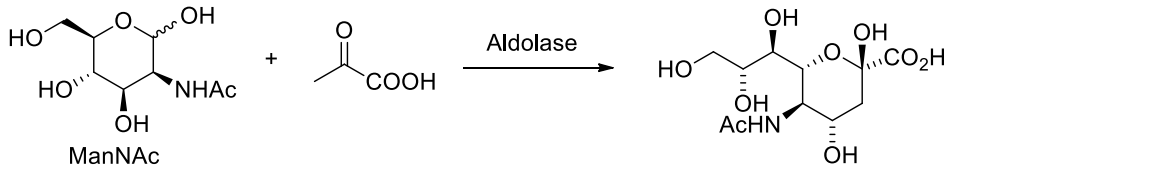


Figure 2.1.2. Chemical synthesis of sialic acids.

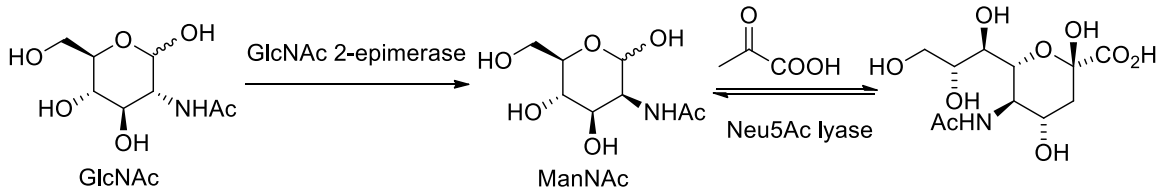
starting material (**Figure 2.1.2**).[45] In 1995, Chan group reported improved method for the direct construction of sialic acid using α–(bromomethyl)acrylic acid and carbonyl compounds mediated by indium in aqueous media.[46] Although the desired sialic acid was constructed concisely, the diastereoselectivity of key allylation reaction was moderate and a large excess of indium (4 equiv) was required for satisfactory reactivity. In 2006, the synthesis of L-Neu5Ac was completed in short steps from L-arabinose by Wong group.[47] Keys to the short synthesis are two C-C bond formations, Petasis vinylation and [3+2] cycloaddition, which are tolerant to free hydroxy groups. In 2011, Crich group [48] reported practical synthesis of 2-keto-3-deoxy-D-glycero-D-galactononulosonic acid (KDN). Using protected sugar derivative as starting material, the key propargylation reaction afforded desired product in good yield and excellent diastereoselectivity, the following bromination, deprotection and ozonolysis afforded KDN in good yield. However, the protection and deprotection processes decreased the overall synthetic efficiency.

Enzymatic methods were also developed for the facile construction of sialic acids. (**Figure 2.1.3**) In 1984, Gautheron group reported the acylneuraminate pyruvate-lyase [49] catalyzed the enzymic reversible condensation of pyruvate with *N*-acetyl-D-mannosamine. The stereoselectivity was controlled by the well-defined structure of enzyme. In 1991, Wandrey group reported an enzymic method for preparing Neu5Ac by reacting inexpensive *N*-acetyl-D-glucosamine (GlcNAc) and pyruvic acid in the presence of Neu5Ac lyase and *N*-acetyl-D-glucosamine 2-epimerase (GlcNAc 2-epimerase) in the enzyme membrane reactor.[50] Compared with ManNAc, GlcNAc was used as less expensive surrogate. Although desired Neu5Ac was obtained in a very efficient manner, the fatal defect of this method was the limitation of GlcNAc 2-epimerase provision. In 1998, Maru group successfully mass-produce GlcNAc 2-epimerase and applied the co-enzyme system for the synthesis of Neu5Ac in an industry scale (23 kg). [51] Later, Hilvert group reported chemoenzymatic synthesis of differentially protected 3-deoxysugars.[52] The macro-phomate synthase (MPS)-catalyzed

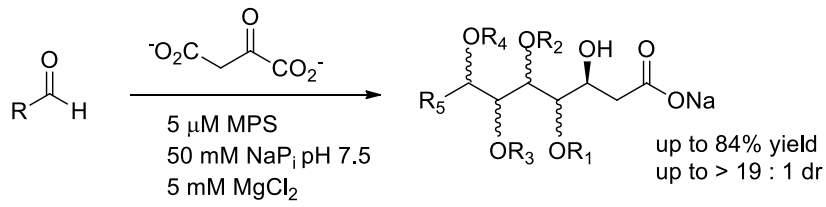
Cornforth reaction with differentially protected aldoses, provided key intermediate for the construction of sialic acid and building blocks for versatile transformation. The discovery and/or engineering of new enzymes for the *R*-configured at anomeric position represented a great challenge. One possible strategy to get access to the enantiomer is taking advantage of enantiocomplementary enzyme strategy, [53] however, great difficulty in enzyme modification and limited substrate applicability hampered the further improvement. General method for the stereodivergent C-C bond forming reaction at anomeric position of unprotected aldoses using artificial catalyst will render general access to versatile chemistry for carbohydrate transformation.

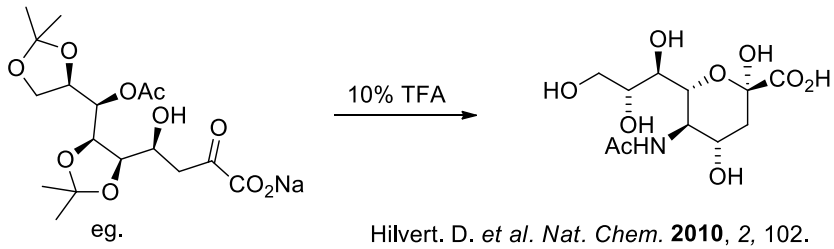


Gautheron, C. *et al. Tetrahedron Lett.* **1984**, *25,* 4663.



Wandrey. C. *et al. Angew. Chem. Int. Ed.* **1991**, *30*, 827.





Hilvert. D. *et al. Nat. Chem.* **2010**, *2,* 102.

Figure 2.1.3. Enzymic synthesis of sialic acids.

To overcome the limitation, I envisaged the use of an asymmetric copper catalyst, capable of controlling the stereochemistry of the C–C bond-formation at the anomeric carbon of unprotected aldoses. The key intermediate could be straightforwardly transformed to sialic acid derivative via oxidation and intramolecular cyclization. Compared with previous methods, no protecting groups were required and a variety of sialic acid derivatives containing different stereoisomer could be synthesized in very efficient manner. (**Figure 2.1.4**)

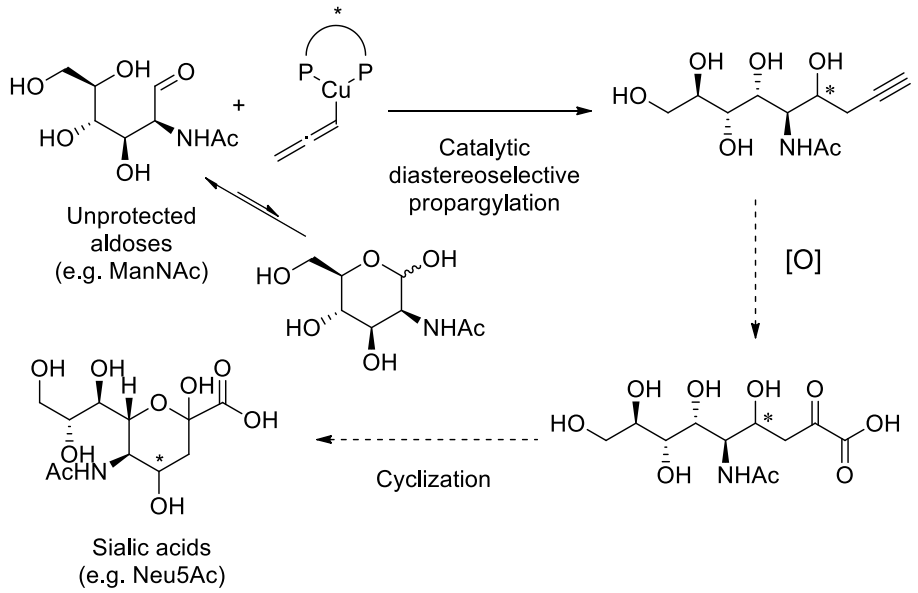


Figure 2.1.4. Strategy for sialic acid synthesis.

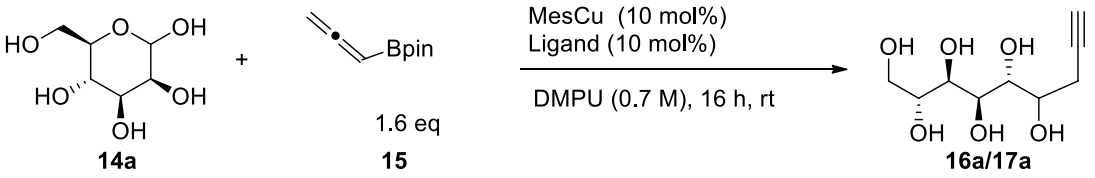
We recently reported a copper(I)-catalyzed anomeric aminoalkynylation of unprotected aldoses (**Figure 1.3.1.6**). [30] In this reaction, the C–C bond-formation is able to proceed in the presence of multiple unprotected hydroxy groups, due to a unique characteristic of the soft organocopper(I) species, [54] which is generated catalytically in situ; namely, the Brønsted basicity is attenuated relative to the nucleophilicity. [29, 33, 34] However, this reaction is limited by the fact that the stereoselectivity is substrate-dependent and not controlled by the catalyst. The results of this study prompted us to speculate that a reaction, proceeding through a cyclic six-membered transition state should render catalyst-controlled stereochemistry more feasible. [10d] Based on this

hypothesis, we investigated a copper-catalyzed anomeric propargylation of unprotected aldoses, wherein the aldehyde forms of the aldoses act, in contrast to the iminium ions in the case of the aminoalkynylation, as the electrophiles.

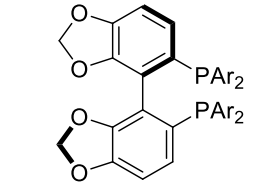
2.2 Development of copper(I) catalyzed stereodivergent propargylation of unprotected aldoses.

2.2.1 Development of novel bidentate phosphine ligand for propargylation of unprotected aldoses

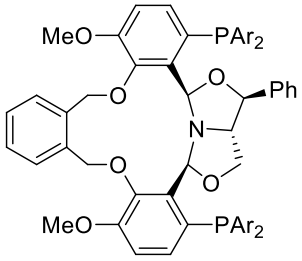
I began investigations using D-mannose (**14a**) and allenylboronate (**15**; 1.6 equiv) as substrates (**Table 2.2.1.1**). The active copper alkoxide catalyst was generated in situ from the reaction of mesitylcopper (MesCu), **14a**, and the corresponding sugar substrate. For initial screening, a variety of commercially available ligands were examined, however, no product was obtained. When Shrimp*, which was originally developed by our group in 2010, [10d] 2% of target material was obtained in low diastereoselectivity.



Entry	Ligand	Yield (%)	*syn* (**16a**): *anti*(**17a**)
1	none	0	-
2	PPh_3	trace	-
3	P(3, 5-CF_3-phenyl)$_3$	trace	-
4	(*S*)-DTBM-SEGPHOS	trace	-
5	Xantphos	trace	-
6	Shrimp*	2	1 : 2.4



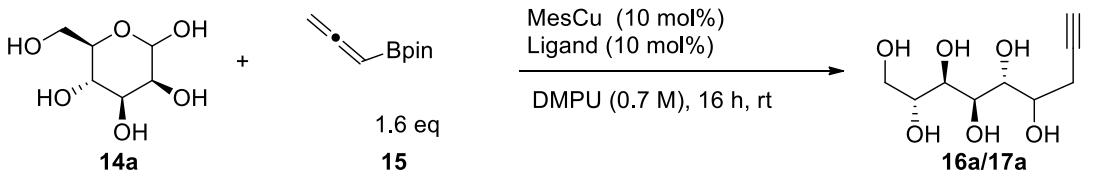
(*S*)-DTBM-SEGPHOS
Ar = (3,5-di-*t*-Bu_2-4-MeO-C_6H_2)



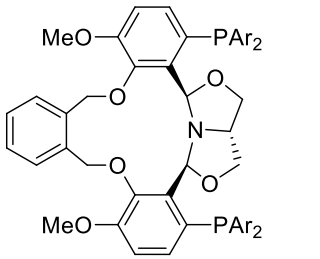
Shrimp*, Ar = *p*-F-C_6H_4
J. Am. Chem. Soc. **2010**, *132*, 6638.

Table 2.2.1.1. Ligand effect.

The shrimp* type of ligands have exceptional large bite angle, which was pivotal to stabilize the monomeric copper catalyst. [55] To minimize the match-mismatch interaction between chiral sugar substrate and chiral shrimp* type ligands, novel achiral ligands were synthesized and further optimization focusing tuning the bulkiness and electron density of the bidentate phosphine ligand was conducted.(**Table 2.2.1.2**) It was found out that by introducing electro-withdrawing bulky CF_3 group at meta-position (**L5**), the reactivity was improved. This result provided me the entry point to the sugar propargylation chemistry.



Entry	Ligand	Yield (%)	*syn* (**16a**): *anti*(**17a**)
1	**L1**	trace	-
2	**L2**	5	1 : 1.9
3	**L3**	trace	-
4	**L4**	3	1 : 1.9
5	**L5**	13	1 : 1.2



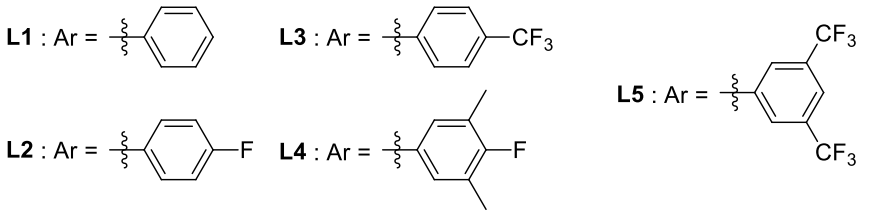
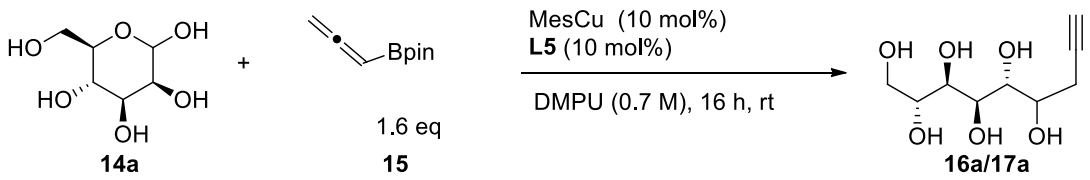


Table 2.2.1.2. Ligand modification.

Next, the metal source effect was examined. (**Table 2.2.1.3**) Without using copper catalyst, no reaction proceeded, this result indicate the importance of copper catalyst for stabilizing the reactive allenyl nucleophile. MesCu showed the best reactivity compared with other copper salts, although the reactivity remained unsatisfactory.



Entry	Cu(I)	LiO*i*-Pr (%)	Yield (%)	*syn* (**16a**): *anti*(**17a**)
1	CuOAc	10	N.R.	-
2	$CuClO_4$•$4CH_3CN$	10	3	1 : 1.6
3	CuCl	10	N.R.	-
4	CuI	10	trace	-
5	$(CuOTf)_2$ •toluene	10	2	1 : 1.4
6	MesCu	-	13	1 : 1.2
7	-	10	N.R.	-

Table. 2.2.1.3. Copper source optimization.

The observed low reactivity should most likely be attributed to the low concentration of the reactive aldehyde form of **14a**.[56] Serianni group reported that the ratio of reactive aldehyde in situ of D-mannose is as low as 0.004% (DMSO as solvent), which means even if high chemoselectivity to distinguish free hydroxyl group and aldehyde could be achieved by using Cu(I) catalyst, it is still a great challenge to catch the trace amount of aldehyde. A proper ring-opening reagent was required to increase the concentration of reactive aldehyde. In this context, Lewis acid metal is considered to be possible choice, since it may reversibly coordinate with sugar substrate and accelerate the ring-opening process via six-membered ring transition state or trap the free hydroxyl group and block the cyclization pathway.

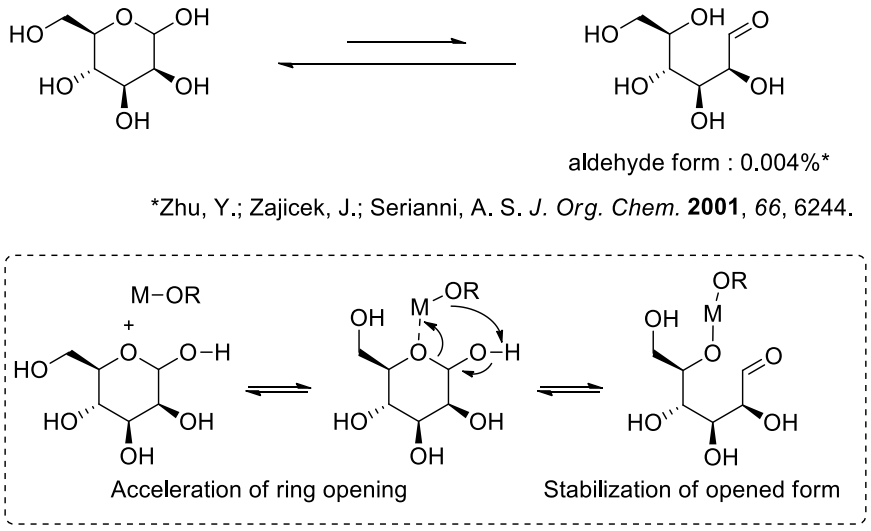
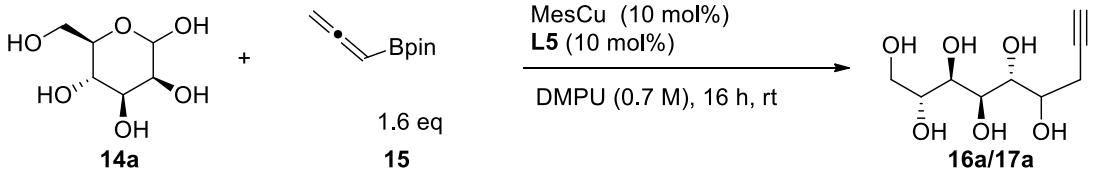


Figure 2.2.1.1. Strategy to increase the concentration of active aldehyde.

A variety of Lewis acid metal was examined, however, no improvement was observed (**Table 2.2.2.4**). A similar strategy, using the combination $B(C_6F_5)_3$ and bulky Lewis base as frustrated Lewis pair, I expected to accelerate the ring opening process (entry 9 and entry 10). However, no reaction proceeded. The use of Lewis acid additive decreased the basicity of the reaction system, thus significantly hampered the transmetalation process. Thus, the further investigation was focused on the reagent with similar Lewis acidity as the allenyl boronate. In this context, borate was considered as an ideal choice, since the Lewis acidity of borate was similar to that of allenylboronate, so the transmetalation process will not be influenced significantly.



Entry	Additive (20 mol%)	Yield (%)	*syn* (**16a**): *anti*(**17a**)
1	$Mg(O\textit{i}\text{-}Pr)_2$	N.R.	-
2	$Zr(O\textit{i}\text{-}Pr)_3$	N.R.	-
3	$Yb(O\textit{i}\text{-}Pr)_3$	N.R.	-
4	$Al(O\textit{t}\text{-}Bu)_3$	N.R.	-
5	CsF	N.R.	-
6	$ZnCl_2$	N.R.	-
7	TBAT	N.R.	-
8	$BF_3 \bullet Et_2O$	N.R.	-
9	$B(C_6F_5)_3$ + $(Mes)_3P$	N.R.	-
10	$B(C_6F_5)_3$ + 2,6-lutidine	N.R.	-

Table 2.2.2.4. Lewis acid effect.

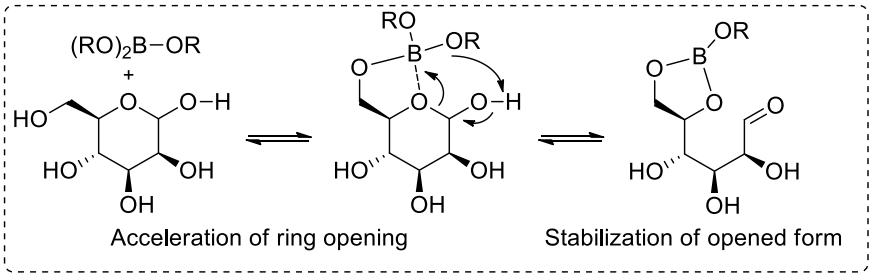


Figure 2.2.1.2. Reaction design using borate as additive.

To testify my hypothesis, NMR experiment was conducted. Without any additive, no aldehyde peak was observed. When 2 equiv. of $B(OMe)_3$ was added, boron-sugar complex was formed and 0.15% of aldehyde peak was observed at 9.66 ppm. And this ratio was 40 times increased compared with the reported one (**Figure 2.2.1.3**). [21]

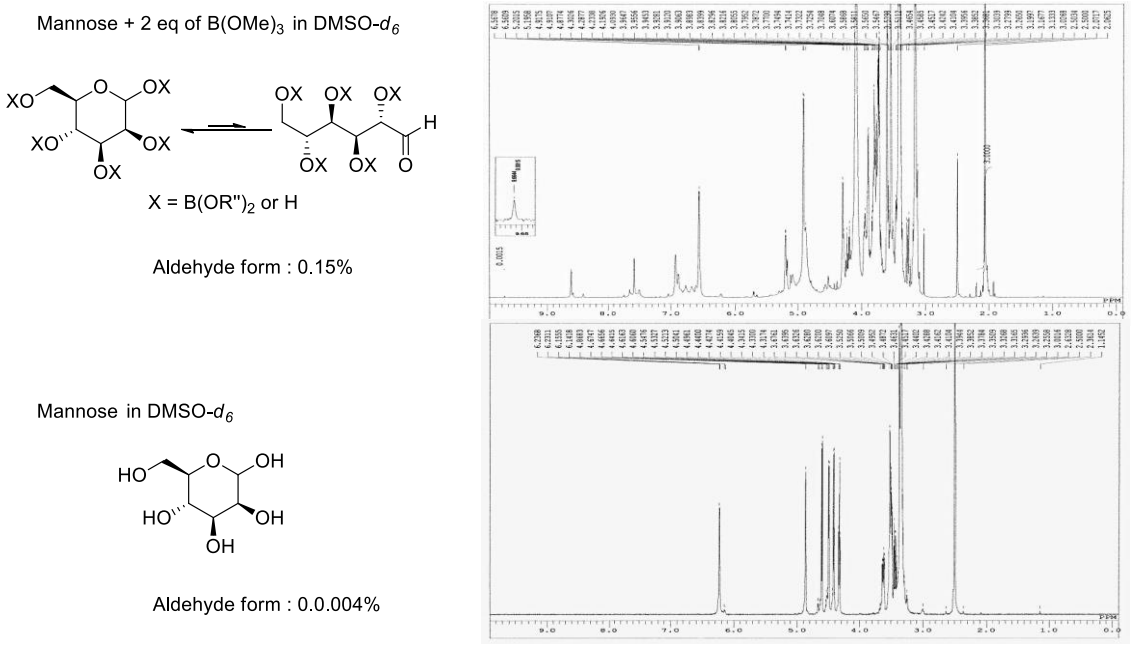
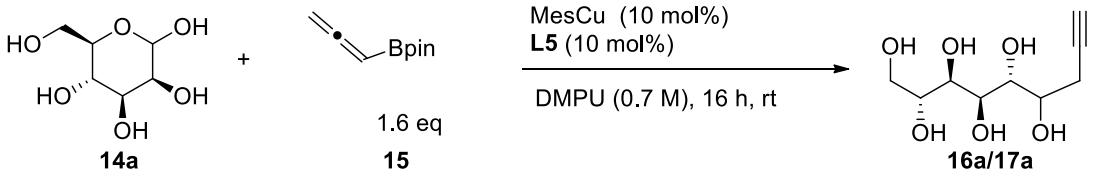
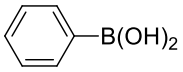
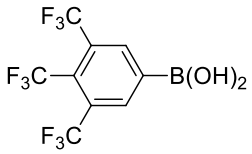
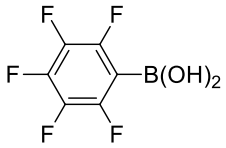
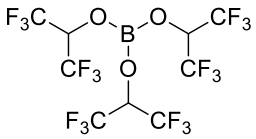
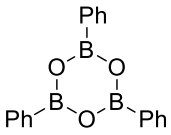
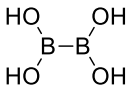


Figure 2.2.1.3. Effect of borate.

Then, the optimization of reaction condition was conducted (**Table 2.2.1.5**). Various boron additives were examined, it was found out that when $B(OMe)_3$ was used as additive (entry 5), the reactivity was improved significantly, the propargylation product was obtained in 38% yield, and the reactivity was further improved by increasing the amount of $B(OMe)_3$ additive (entry 6). While the use of pentafluorophenylboronic acid dramatically improved the diastereoselectivity, the reactivity decreased (entry 9).

Although only moderate yield and diastereoselectivity was achieved using the originally developed catalyst, the investigation identified a proper ring-opening reagent which dramatically increased the reactive aldehyde concentration. In addition, the identification of bite angle effect of novel bidentate phosphine ligand indicated future direction for further investigation.



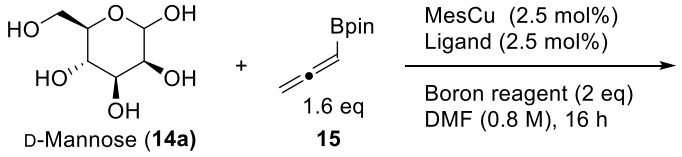
Entry	Additive (100 mol%)	Yield (%)	*syn* (**16a**): *anti*(**17a**)
1	-	13.	1 : 1.2
2	*i*-PrO-Bpin	20	1 : 1.2
3	EtO-Bpin	19	1 : 1.3
4	MeO-Bpin	7	1 : 1.6
5	$B(OMe)_3$	38.	1 : 2
6[a]	$B(OMe)_3$	53	1 : 2.3
7		16	1 : 1.6
8		2	1 : 1.3
9		12	1 : 5.1
10		trace	-
11		2	1 : 2.9
12		8	1 : 2.2

a. 2 eq of $B(OMe)_3$ was used.

Table. 2.2.1.5. Optimization using borate or boronic acid as additive.

2.2.2 Copper(I) catalyzed stereodivergent propargylation of unprotected aldoses.

Based on the previously result, the further optimization of the reaction condition was conducted using DMF as solvent. While the addition of boric acid[17] did not improve the reactivity (entry 3), addition of $B(OMe)_3$ promoted the desired reaction, affording **16a** and **17a** in a combined yield of 17% (3:1 diastereoisomer ratio) in the presence of 2.5 mol% of an achiral Cu-Xantphos catalyst (entry 4). Although the use of chiral ligands, such as DTBM-SEGPHOS (**L6**; entries 5 and 6), BINAP (**L7**; entries 7 and 8), and Ph-BPE (**L8**; entries 9 and 10) did not induce significant diastereoselectivity, Ph-SKP (**L9**) [57] turned out to be exceptional. The use of (*S,S,S*)-**L9** (entry 11) furnished the *si*-face



Entry	Boron reagent	Ligand	Yield (%)	**16a** : **17a**
1	none	none	0	-
2	none	Xantphos	trace	-
3	$B(OH)_3$	Xantphos	trace	-
4	$B(OMe)_3$	Xantphos	17	3 : 1
5	$B(OMe)_3$	(*S*)-**L6**	8	1 : 1
6	$B(OMe)_3$	(*R*)-**L6**	7	1 : 1
7	$B(OMe)_3$	(*S*)-**L7**	36	1 : 1
8	$B(OMe)_3$	(*R*)-**L7**	38	1 : 1
9	$B(OMe)_3$	(*S,S*)-**L8**	43	4 : 1
10	$B(OMe)_3$	(*R,R*)-**L8**	50	1 : 1
11	$B(OMe)_3$	(*S,S,S*)-(–)-**L9**	95	> 20 : 1
12	$B(OMe)_3$	(*R,R,R*)-(+)-**L9**	84	1 : > 20

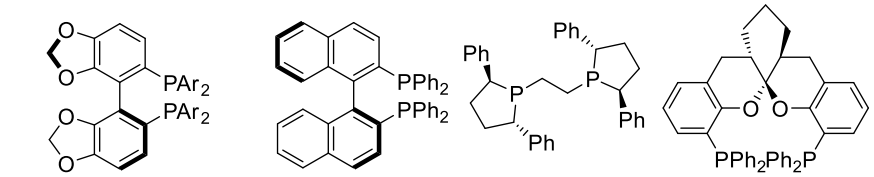


Table 2.2.2.1. Optimization of the stereodivergent propargylation of D-Mannose.

adduct **16a** in high yield and excellent diastereoselectivity, while using (*R*,*R*,*R*)-**L9** (entry 12) predominantly afforded the *re*-face adduct **17a**. Thus, both diastereomers, **16a** and **17a**, were accessible selectively in high yield and stereodivergency, simply by switching the absolute configuration of the chiral copper catalyst.

A proposed catalytic cycle for this process is shown in **Figure 2.2.2.1**. Initially, copper alkoxide **A** should be generated from the deprotonation of an aldose hydroxy group by MesCu. Subsequently, **A** should undergo transmetalation with the allenylboronate **15** to produce allenylcopper **B** as the active species. The concentration of the reactive aldehyde **C**, in equilibrium with the cyclic hemiacetal form of the aldose, would be increased by the addition of $B(OMe)_3$. This should favor the stabilization of the aldehyde form through the formation of reversible covalent bonds between the hydroxy groups of the aldose. Thus, the C–C bond-forming reaction would proceed via a six-membered transition state, **D**, to afford copper alkoxide **E**. Finally, transmetalation

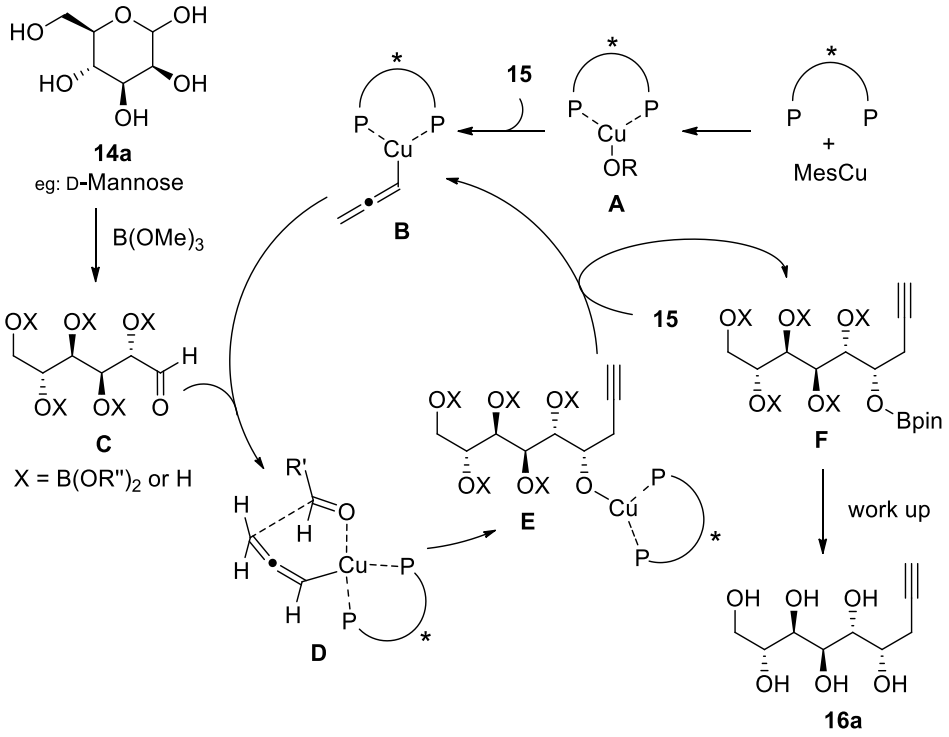
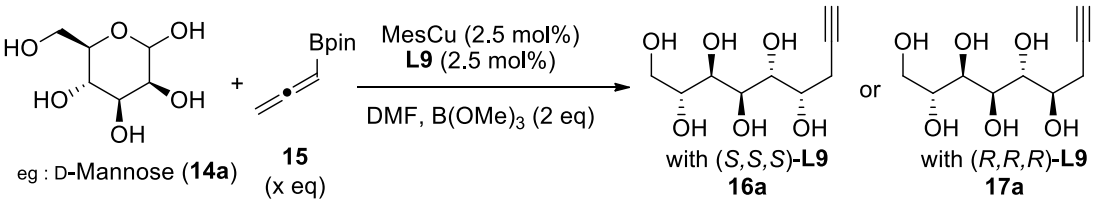


Figure 2.2.2.1. Proposed catalytic cycle for the catalyst-controlled stereodivergent propargylation of unprotected aldoses.

between **E** and **15** would regenerate allenylcopper species **B**. Subsequent cleavage of the O–B bond in **F** during the work-up would provide the desired product **16a**.

Having established optimal conditions for this highly diastereoselective propargylation, I next examined the substrate scope (**Table 2.2.2.2**). Using ligands with either (*S*,*S*,*S*)- or (*R*,*R*,*R*)-configuration, the reaction proceeded in high yield and excellent diastereoselectivity with a variety of aldoses, including five-carbon aldoses (D-lyxose, D-arabinose and D-xylose) and six-carbon aldoses (D-mannose, D-glucose and D-galactose) (entries 1-12). Relative to other aldoses, glucose (**14c**) was less reactive, presumably due to the formation of a stable cyclic hemiacetal, wherein all the substituents on the tetrahydropyran ring occupy equatorial positions. The concentration of the reactive aldehyde thus remains very low, even in the presence of $B(OMe)_3$. Nevertheless, increasing the amount of 2 to 5 equiv and the reaction temperature to 60 °C furnished **16c** and **17c** in good yield, albeit with moderate diastereoselectivity for **17c** (entries 5 and 6).



eg : D-Mannose (**14a**) | **15** (x eq) | with (*S,S,S*)-**L9** **16a** | with (*R,R,R*)-**L9** **17a**

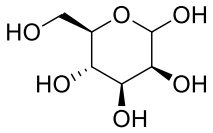
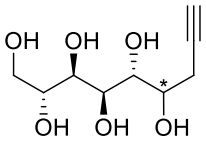
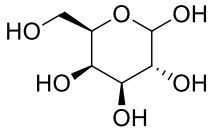
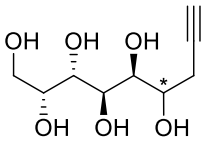
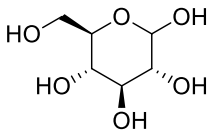
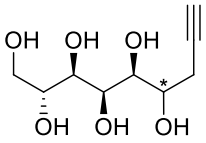
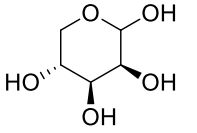
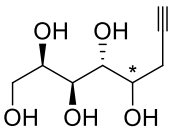
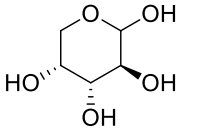
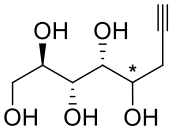
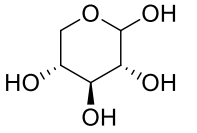
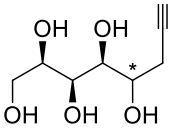
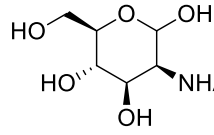
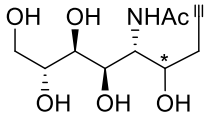
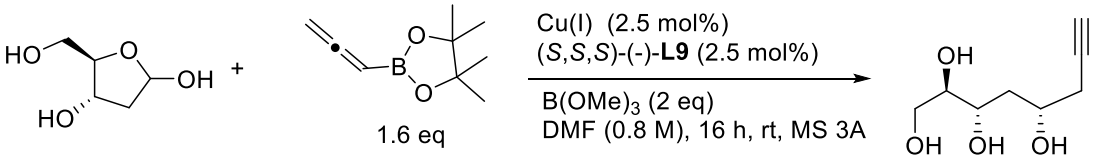
Entry	Substrate	x	Product	Yield (%),[a] dr[b] with (*S,S,S*)-**L9** or (*R,R,R*)-**L9**
1 2	 D-Mannose (**14a**)	1.6		**16a**: 90%, >20:1 **17a**: 81%, 1:>20
3[c,d] 4[c,d]	 D-Galactose (**14b**)	3		**16b**: 73%, 11:1 **17b**: 66%, 1:9.2
5[c,e,f] 6[c,e,f]	 D-Glucose (**14c**)	5		**16c**: 76%, >20:1 **17c**: 72%, 1:3.5
7 8	 D-Lyxose (**14d**)	1.6		**16d**: 84%, >20:1 **17d**: 81%, 1:>20
9 10	 D-Arabinose (**14e**)	1.6		**16e**: 95%, >20:1 **17e**: 93%, 1:>20
11[c,d] 12[c,d]	 D-Xylose (**14f**)	1.6		**16f**: 65%, >20:1 **17f**: 60%, 1:>20
19[c] 20[c]	 *N*-Acetyl-D-Mannosamine (**14g**)	3		**16g**: 70%, >20:1 **17g**: 51%, 1:>20

Table 2.2.2.2. Substrate scope of the stereodivergent propargylation of unprotected aldoses. [a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] MS 3A was added. [d] The reaction was carried out at 40 °C. [e] The reaction was carried out at 60 °C. [f] $B(OMe)_3$ (6 equiv) was added.

I also found that condition A was not suitable for 2-deoxy-aldoses, probably due to a faster protonolysis of allenylcopper **B** relative to the desired C–C bond-formation. As a consequence, we decided to re-examine milder reaction conditions, with the aim of decreasing the concentration of the in situ-generated allenylcopper species (**Table 2.2.2.3**). During this examination, we observed that the combination of $CuClO_4(MeCN)_4$ and CF_3COOK generates the milder Brøsted base CF_3COOCu, which proved effective for the propargylation of 2-deoxy-aldoses.

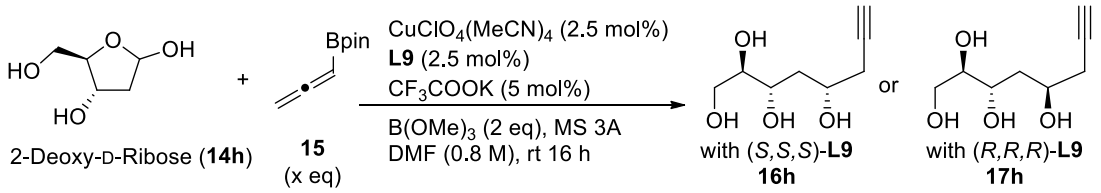


14h **15** **16h**

Entry	Copper source	Base (5 mol%)	Yield (%)	*syn* : *anti*
1	MesCu	-	48	> 20 : 1
2	$CuClO_4(MeCN)_4$	KOAc	trace	3 : 1
3	$CuClO_4(MeCN)_4$	PhCOONa	trace	1 : 1
4	$CuClO_4(MeCN)_4$	Cesium pivalate	trace	1 : 1
5	$CuClO_4(MeCN)_4$	CF_3SO_3Na	trace	1 : 1
6	$CuClO_4(MeCN)_4$	KOAc	trace	1 : 1
7	$CuClO_4(MeCN)_4$	CF_3COOK	65	18 : 1

Table 2.2.3. Optimization for 2-deoxy-aldoses

Upon applying optimized condition, both five- and six-carbon 2-deoxy-aldoses (2-deoxy-D-ribose, 2-deoxy-D-galactose, 2-deoxy-D-glucose) afforded the corresponding products in good yield (entries 1-6). The substrate was further extended to *N*-acetyl-D-galactosamine and *N*-acetyl-D-glucosamine (entries 7-10) using a slightly modified version (increased amount of Cu salt and using DMPU as the solvent).



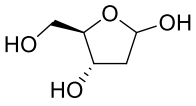
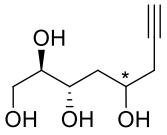
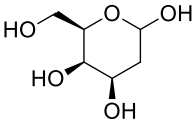
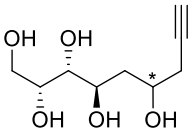
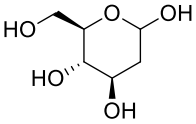
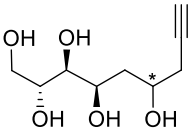
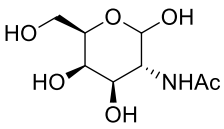
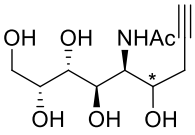
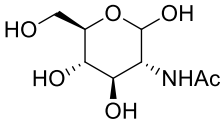
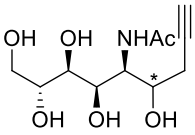
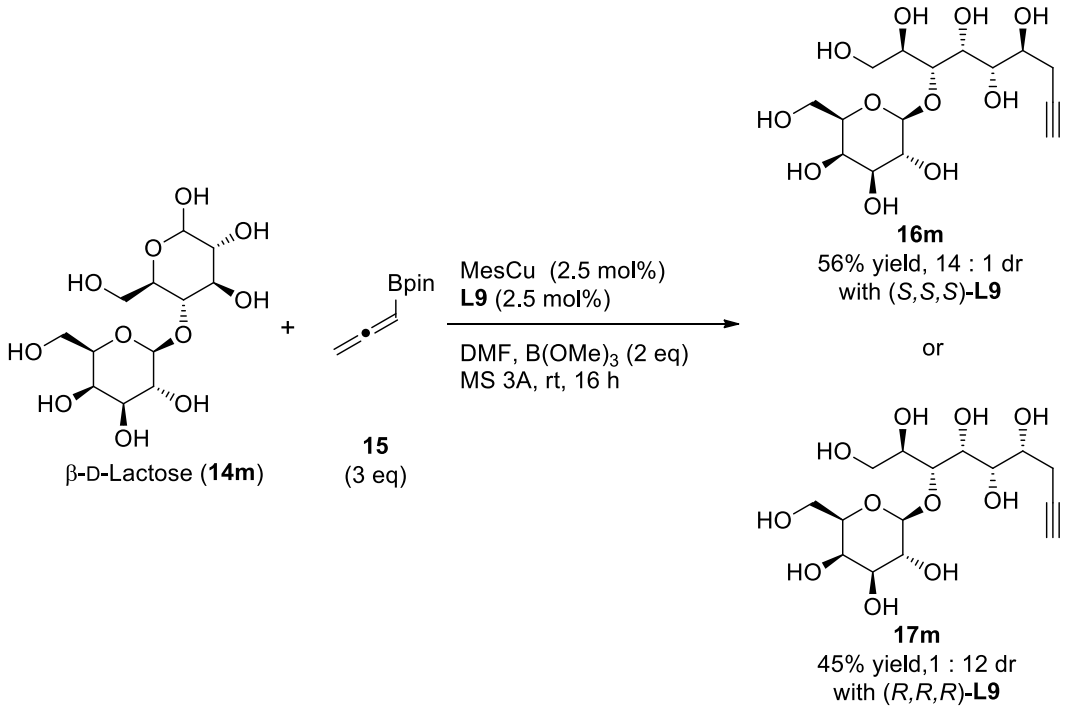
Entry	Substrate	x	Product	Yield (%),[a] dr[b] with (*S,S,S*)-**L9** or (*R,R,R*)-**L9**
1 2	 2-Deoxy-D-Ribose (**14h**)	3		**16g**: 65%, 18:1 **17g**: 53%, 1:>20
3 4	 2-Deoxy-D-Galactose (**14i**)	3		**16h**: 74%, >20:1 **17h**: 67%, 1:10
5 6	 2-Deoxy-D-Glucose (**14j**)	3		**16i**: 59%, >20:1 **17i**: 52%, 1:17
7[c,d] 8[c,d]	 *N*-Acetyl-D-Galactosamine (**14k**)	5		**16k**: 55%, >20:1 **17k**: 40%, 1:>20
9[c,d] 10[c,d]	 *N*-Acetyl-D-Glucosamine (**14l**)	5		**16l**: 45%, 15:1 **17l**: 51%, 1:>20

Table 2.2.2.4. Substrate scope of the stereodivergent propargylation of unprotected aldoses. [a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] The reaction was carried out at 40 °C. [d] 3.8 mol% of $CuClO_4(MeCN)_4$ and 2.5 mol% of **L9** were used; $B(OMe)_3$ was decreased to 1.5 eq and DMPU was used as the solvent. Isolated yields and diastereoisomer ratios were determined after the conversion of the products to the poly-benzoylated compounds.

Notably, the reaction with the disaccharide-D-lactose (**14m**) proceeded smoothly under condition A to give **16m** and **17m** in good yield and excellent diastereoselectivity (**Scheme 2.2.2.1**). The high tolerance to multiple free hydroxyl groups, and the outstanding stereoselectivity made the developed reaction a general method for the facile construction of polyol-containing terminal alkyne moieties.



Scheme 2.2.2.1. Stereodivergent propargylation of β-D-lactose.

2.3 Aqueous phase synthesis of sialic acid without using protecting groups.

Once the desired propargylation products were obtained, we tackled the synthesis of the corresponding sialic acid derivatives, starting by optimizing the synthesis of KDN from **14a**. In order to achieve environmentally benign synthesis, the synthetic route was designed using H_2O as sole solvent and no protecting group was required to assist the transformation. The propargylation of D-mannose proceeded smoothly on a 1.8 g-scale using as little as 0.2 mol% of (*S*,*S*,*S*)-**L9**/MesCu. After quenching with MeOH, the mixture was concentrated. The crude solid was washed successively with EtOAc and MeOH to provide **16a** in 87% yield and >20:1 diastereoselectivity. With a sufficient amount of key intermediate **16a** in hand, we subsequently examined the chemoselective oxidation of the C–C triple bond to give an α-keto carboxylic acid group (**Table 2.3.1**). The consecutive two-fold bromo-oxygenation of the C–C triple bond (one intramolecular and one intermolecular) proceeded effectively by a short (10 min) treatment of **16a** with Br_2 in aqueous solution to afford **18a**, which contains a pyranose skeleton. Subsequently, the dibromomethane moiety was converted into the corresponding hydrate of the formyl group by hydrolysis under basic aqueous conditions (1 h). Finally, a short (5 min) Pinnick oxidation furnished the targeted natural KDN (**19a**) in 76% overall yield. Following the same sequence, another relevant natural sialic acid, Neu5Ac (**19g**), and its unnatural C4-epimer (**19g`**) were synthesized from **16g** and **17g**, respectively. Since the propargylation proceeded with five-carbon aldoses, an unnatural eight-carbon analogue of sialic acid (**19d**) was also accessible starting from lyxose. The robustness of this synthetic method is illustrated by the conversion of **17m** into **19m**: unnatural disaccharide 6m, containing a sialic acid residue at the reducing end, was also obtained in high yield using modified bromooxygenation conditioin (KBr + Oxone) [58] followed by hydrolysis and Pinnick oxidation.

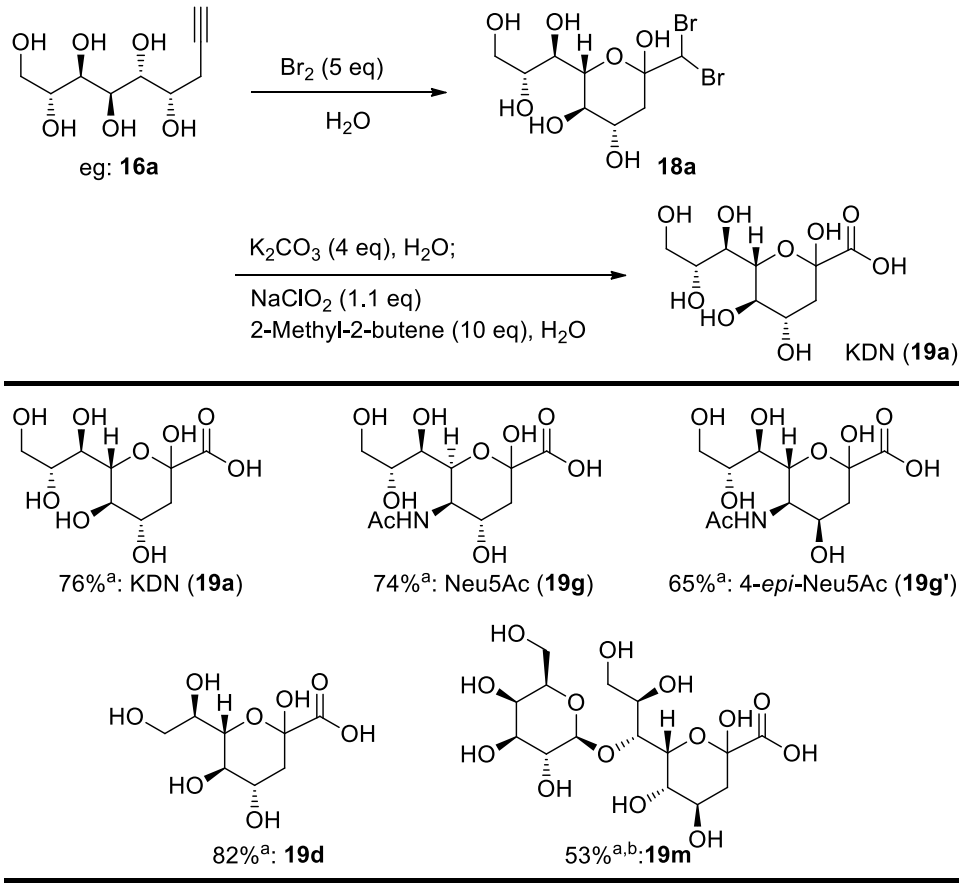


Table 2.3.1 [a.]Isolated yield after the three-step conversion were described.[b.]KBr and oxone were used instead of Br_2 for bromooxygenation

2.4 Summary

In conclusion, I have developed a practical and short (four steps) synthetic route to various sialic acid derivatives, starting from readily available aldoses. The overall sequence does not require any protecting groups, and the oxidation states constantly increase.[59] Key to the success of this method is the copper-catalyzed stereodivergent propargylation, in which unprotected aldoses can be used. Even in the presence of a large excess of protic species and/or functional groups, the catalytically generated allenylcopper(I) species exhibits remarkable stability against protonolysis, still retaining high reactivity as a polar carbon nucleophile towards aldehydes. This unique characteristic is most likely due to the orthogonal reactivity between the soft allenylcopper(I) species and the hard hydroxy groups. Despite the complex chiral environments with multiple hydroxy groups present in the substrates, the diastereoselectivity of this process is controlled by the asymmetric catalyst. Subsequently, the propargylation products can be transformed into sialic acid derivatives via a simple three-step sequence. In addition, we successfully transformed the reducing end of a disaccharide into a sialic acid derivative selectively (from **17m** to **19m**); such reactivity should easily find applications in the artificial late-stage modification of sugar chains at the reducing end. The synthetic method reported herein offers general and straightforward access to a wide variety of sialic acid derivatives, and thus promises great potential in the context of drug discovery and investigations of biological functions.

3. Ligand-Controlled Copper(I)-Catalyzed Regiodivergent Synthesis of Conjugated and Skipped Ene-ynes

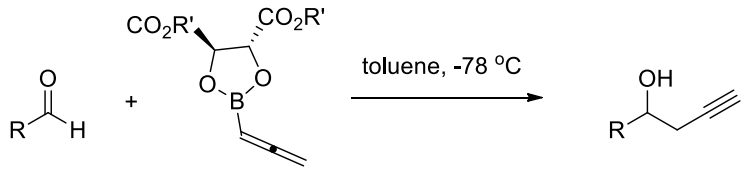
3.1 Introduction

Alkyne moiety is prevalent in biologically active natural products and pharmaceutical compounds and also a versatile precursor for various functional groups. The direct generation of carbanion equivalents from readily accessible alkynes, especially in a catalytic manner, for the selective addition to carbonyl compounds will bring about significant improvement in carbanion chemistry.

In 1950, Prévost et al. discovered that allenic Grignard reagents could react with carbonyl compounds with the generation of mixtures of α–allenic and β-acetylenic carbinols. [60] Since then, pre-formed organometallic reagents such as boron,[61]silicon,[62] tin, [63] lithium, [64] aluminum, [65] zinc, [66] titanium [67] reagents were applied to the propargylation of carbonyl compounds.

In 1982, the first enantioselective propargylation of carbonyl compounds was reported by Yamamoto and co-workers. (**Figure 3.1.1**) Using 2,4-dimethyl-3-pentanol derived chiral allenyl-boronate as nucleophile, excellent regioselectivity and enantioselectivity were achieved for propargylation of various aldehydes. [68] Since then, the use of chiral allenyl prenucleophile as propargyl donor was extensively studied. Corey group [69], Marshall group, [70] Hayashi group, [71] Soderquist group [72] and Panek group [73] further expanded the scope of chiral prenucleophiles. Although satisfactory reactivity and enatioselectivity were achieved, the requirement of multiple additional steps for the preparation of the reactive chiral prenucleophiles limited the overall synthetic efficiency.

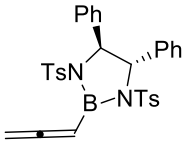
As an alternative, utilization of external chiral source to govern the asymmetric propargylation reaction provides a way around these limitations. In 1987, Mukaiyama group reported asymmetric propargylation of aldehyde with allenic aluminum using



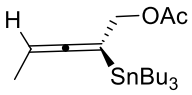
R' = 2,4-dimethyl-3-pentyl

67-90% yield
92-99% ee

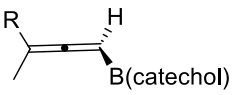
Yamamoto.H. *et al*. *J. Am. Chem. Soc.* **1982**, *104*, 7667.



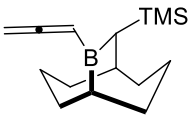
Corey. E. J.
J. Am. Chem. Soc.
1990, 878



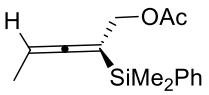
Marshal. J. A.
J. Org. Chem.
1991, 3211



Hayashi. T.
J. Chem. Soc. Chem. Commun.
1993, 1468



Soderquist. J. A.
Org. Lett.
2005, 799

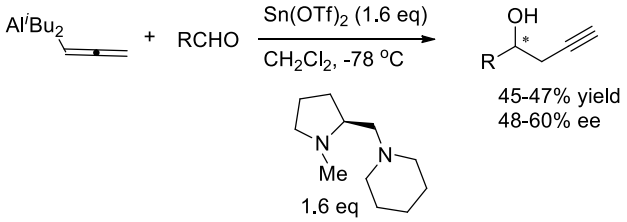


Panek. J. S.
Org. Lett.
2007, 2689

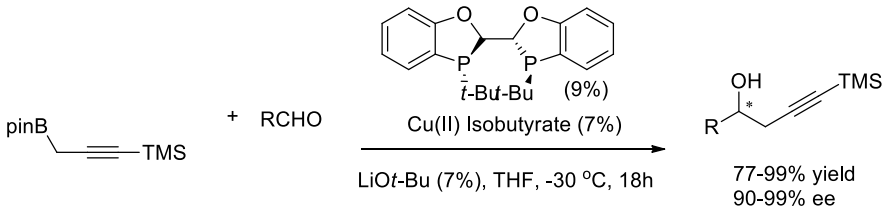
Figure 3.1.1. Selected examples for enantioselective carbonyl propargylation using chiral nucleophiles.

excess chiral diamine ligand and tin triflate. (**Figure 3.1.2**) However, only moderate yield and enantioselectivity was achieved. [74] Based on this fundamental research, the concept was further expanded to the catalytic reactions. Allenyl tin reagents, [75] allenyl silicon reagents[76]as well as propargyl boron reagents[10d, 77] are widely applied to this chemistry. In 2010, Senanayake group reported copper-catalyzed enantioselective propargylation of a variety of aldehydes, high yield and excellent enantioselectivity were achieved using an air-stable bidentate phosphine ligand (BIBOP). [78] At same time, enantioselective propargylation of ketone substrates, which is more challenging than aldehydes in terms of both reactivity and stereoselectivity, was achieved by Shibasaki and Kanai group.[10d] By identifying novel bidentate phosphine with large bite angle,

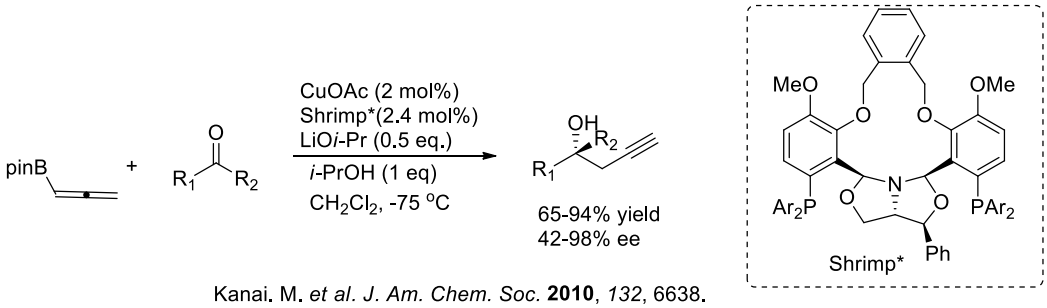
high yield and excellent enantioselectivity were achieved. The soft copper nucleophile remained high nucleophilicity even in the presence of protonic additive (*i*PrOH). The concept was further extended to the stereodivergent propargylation of unprotected sugars (described in **chapter 2**), enabling propargylation reaction with high functional group tolerance as well as excellent stereocontrol ability with substrate containing complex internal chiral environment. [76g]



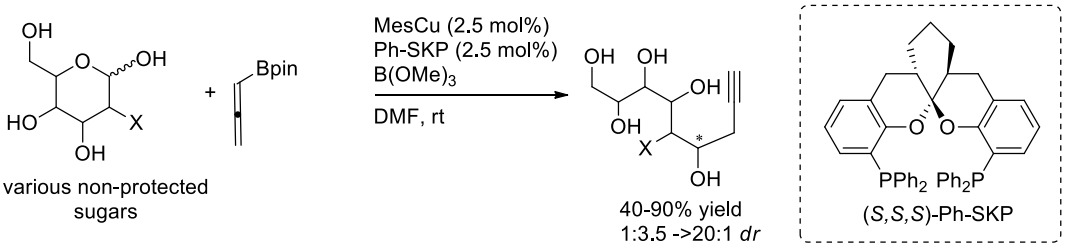
Mukaiyama. T. *et al. Bull. Chem. Soc. Jpn*. **1987**, *60*, 3697.



Senanayake. C. H. *et al. J. Am. Chem. Soc.* **2010**, *132*, 7600.



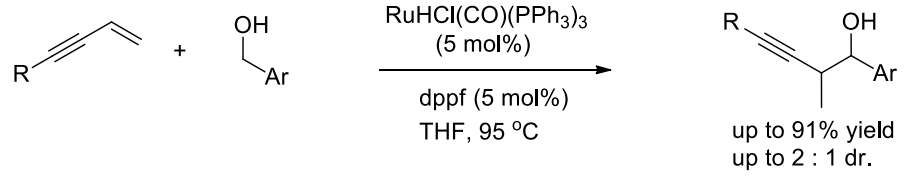
Kanai. M. *et al. J. Am. Chem. Soc.* **2010**, *132*, 6638.



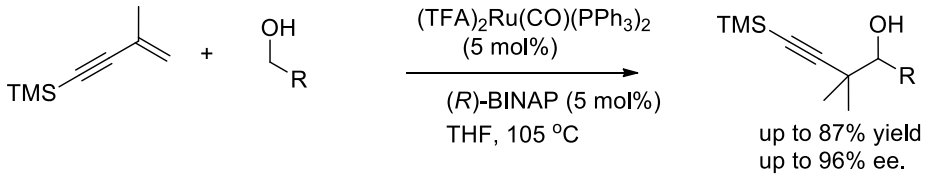
Kanai. M. *et al. ACS Cent Sci.* **2016**, *2*, 21.

Figure 3.1.2. Selected examples for catalytic enantioselective carbonyl propargylation.

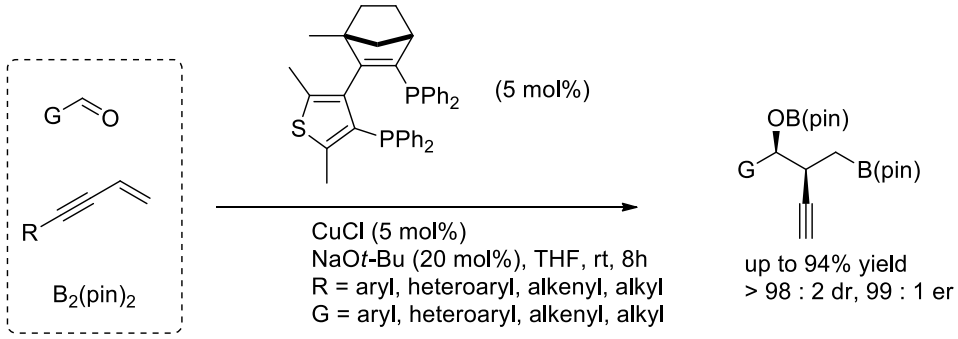
Although significantly improved synthetic efficiency was achieved by limiting the use of protecting group as well as increasing the catalyst efficiency, the developed methodology still required pre-activated reagents, and the stoichiometric waste (XBpin), generated during the reaction, hampered the overall atom-economy. To overcome the limitation and further expand the application scope, novel strategy to generate reactive propargylic anion intermediate will be of great importance.



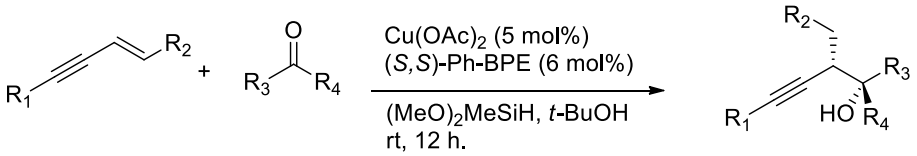
Krische. M. J. *et al*. *Angew. Chem. Int. Ed.* **2008**, *47*, 5220.



Krische. M. J. *et al*. *J. Am. Chem. Soc.* **2016**, *138*, 5238.



Hoveyda. A. H. *et al*. *J. Am. Chem. Soc.* **2014**, *136*, 11304.



Buchwald. S. L. *et al*. *Science.* **2016**, DOI: 10.1126/science.aaf7720.

Figure 3.1.3. Selected examples for catalytic generation of propargylic anion intermediate from stable prenucleophile.

In 2008, Krische reported novel approach to generate propargylic anion intermediate via ruthenium-catalyzed transfer hydrogenation (**Figure. 3.1.3**). [79] The developed methodology enabled carbonyl propargylation from the alcohol oxidation level without using preformed allenylmetal reagents. Good yield was achieved, although the diastereoselectivity was not satisfactory. Enantioselective version of the reaction was achieved by using TMSC ≡ CC(Me)=CH_2 as nucleophile, which construct one stereogenic center. [80]

In 2014, Hoveyda group [81] reported copper catalyzed enantioselective multicomponent process for the construction of compounds containing a primary C-B(pin) bond, as well as alkyne and hydroxyl –substituted tertiary carbon stereogenic centers. The propargylic copper intermediate, generated via enantioselective addition of in situ generated (ligand)Cu-B(Pin) to the alkene of 1,3-enyne, was key for the successful transformation. The developed process introduced additional functional group along with the formation of chiral center, provided important intermediate for versatile transformation.

In 2016, Buchwald group[82] reported copper-catalyzed asymmetric addition of olefin-derived nucleophiles to ketones. The propargylic copper intermediate, generated via enantioselective addition of copper hydride across the C=C double bound, served as key intermediate for the nucleophilic addition to ketones. High yield and excellent level of enantioselectivity was achieved. The high tolerance to functional group made the developed method capable for late stage modification of complex moieties.

Although the above mentioned methodology enabled direct generation of propargylic anion intermediate with the assistance of additional stoichiometric activation reagent (boron or hydride), catalytic direct deprotonation of propargylic C-H bond followed by C-C bond formation remain undeveloped. By taking advantage of Hard-Soft mismatch characteristic of hard anion conjugated soft copper catalyst (described in **chapter 1**), our group have achieved general method for the generation of a variety of soft copper nucleophiles. The unique property of copper catalyst enable the deprotonation of

challenging substrates, even acetonitrile (pK_a in DMSO is 31.3) was successfully deprotonated with the generation of an enolate equivalent [16, 83]. The soft-soft interaction between heteroatoms (such as sulfur, nitrogen, or oxygen) polarized the α-C-H bond and accelerated the proton transfer process. While the concept was widely applied to carbonyl chemistry, up to now, has not been applied to alkynes lacking electron withdrawing groups.

The propargylic proton is weakly acidic with an estimated pK_a value in DMSO > 30 for propyne. [84] It is generally deprotonated using strong base such as *t*-BuLi and *n*-BuLi at low temperature (**Figure 3.1.4**). [85] Using mild base for the deprotonation, similar as the soft enolization of carbonyl compounds, will give access to the functional group tolerated versatile transformation at propargylic position.

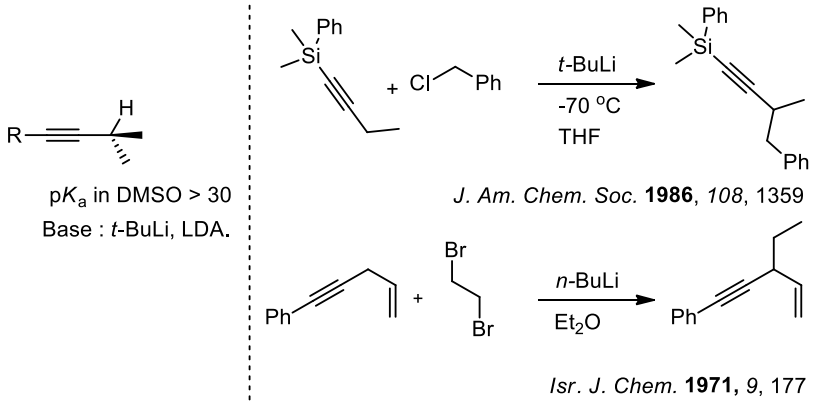


Figure 3.1.4. Propargylic deprotonation.

3.2 Development of ligand-controlled copper(I)-catalyzed regiodivergent synthesis of conjugated and skipped ene-ynes.

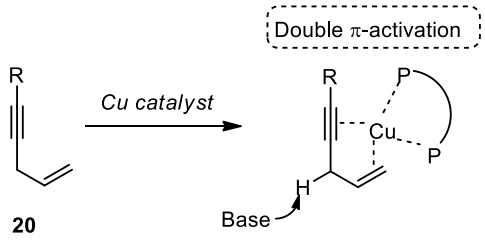
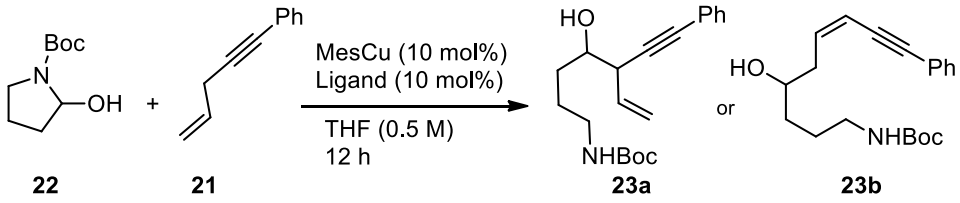


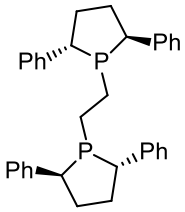
Figure 3.2.1. Reaction design.

My working hypothesis is shown in **Figure 3.2.1**. I expect that the copper catalyst will interact with skipped ene-yne and enable the deprotonation process via the novel "double π-activation" using mild base. Following this concept, readily available skipped ene-yne **21** (**Figure 3.2.2**) as a substrate, the nucleophilic addition was expected to proceed even in the presence of free hydroxyl group of cyclic hemiaminal (**22**). Although the use of simple achiral phosphine ligands showed negative results, the use of bulky (*S*)-DTBM-SEGPHOS furnished the terminal adduct **23b** in high yield with excellent regioselectivity and *cis/trans* selectivity, while using SS_{906}, the product **23a** was obtained in high regioselectivity. The enantioselectivity of this reaction was not satisfactory (**23a** : 0% ee (ligand: SS_{906}), **23b** : 26% ee (ligand: (*S*)-DTBM-SEGPHOS)).

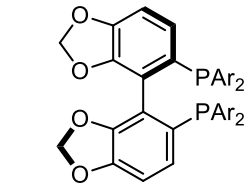


22 **21** **23a** **23b**

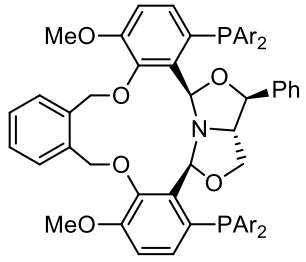
Entry	Ligand	Yield (%)	**23a** (dr) : **23b** (*cis* : *trans)*
1	PPh_3	trace	ND
2	dppm	trace	ND
3	dppe	trace	ND
4	dppp	< 5	ND
5	Xantphos	trace	ND
6	Ph-BPE	40	1 : > 20 (> 20 : 1)
7	(*S*)-DTBM-SEGPHOS	95	1 : > 20 (> 20 : 1)
8	SS_{906}	46	> 20 (1.1 : 1) : 1



(*S,S*)-Ph-BPE



(*S*)-DTBM-SEGPHOS
Ar = (3,5-di-*t*-Bu_2-4-MeO-C_6H_2)



SS_{906}, Ar = C_6H_5
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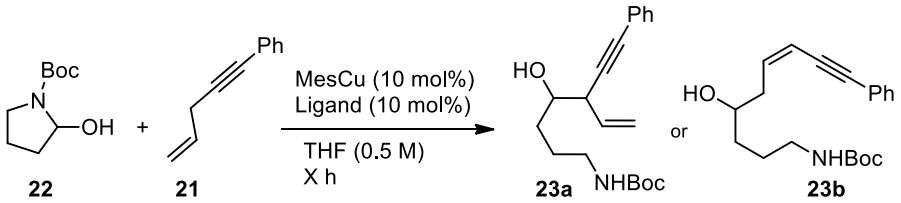
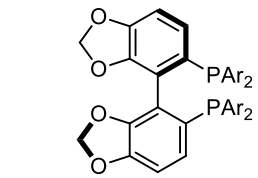
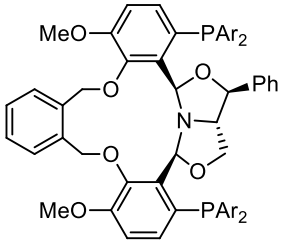
Table 3.2.1. Optimization of the reaction condition

To understand the reason for the regioselectivity, thermodynamic experiment was conducted (**Table 3.2.2**). When (*S*)-DTBM-SEGPHOS was used as ligand, the ratio of product **23b** increased from **23a**/**23b** = 1/4 to 1/>20 as the reaction proceeded. This result indicates that the nucleophilic attack from internal carbon of the ene-yne was reversible, and the kinetically favored product **23a** was constantly transformed to thermodymically stable product **23b** as the reaction proceeded. When SS_{906} was used as ligand, remarkable regio-selectivity was observed and only product **23a** was obtained even after longer reaction time. This result indicates unique character of SS_{906}.





(*S*)-DTBM-SEGPHOS
Ar = (3,5-di-*t*-Bu_2-4-MeO-C_6H_2)



SS_{906}
Ar = C_6H_5

time	yield		ratio (**23a**/**23b**)
	23a	**23b**	
3 h	8%	31%	1/4
12 h	0%	95%	1/>20

time	yield		ratio (**23a**/**23b**)
	23a	**23b**	
3 h	37%	0%	>20/1
12 h	45%	0%	>20/1

Table 3.2.2. Thermodynamic experiment

Using (*S*)-DTBM-SEGPHOS as ligand, the substrate scope was investigated (**Figure. 3.2.2**). For nucleophile investigation, ene-yne compounds embedded with indole moiety (**24)**, electron-donating group (**25**) could be applicable to the reaction. The developed method could also be applied to the 8-membered (**26**) and 6-membered cyclic hemiaminals (**27**) and a 6-membered hemiacetal (**28**). The corresponding target products were obtained in high yield and excellent regio- and *cis/trans* selectivity.

When SS_{906} was used as ligand, **23a** was dominant, while the diastereoselectivity was poor. Initial investigation identified that CF_3CH_2OH was efficient additive to increase the *dr* from 1.1/1 to 2.5/1 (entry 1 and entry 2, **Figure. 3.2.3**), while prolonging the reaction decreased the diastereoselectivity. (entry 2 and entry 3). This result indicated that the nucleophilic attack process was reversible even with Cu(I)/SS_{906} catalyst, and the diastereoselectivity dropped as the reaction proceeded. Further investigation,

including *in-situ* trapping the free hydroxyl group of product, or identify milder reaction which would significantly suppress the retro-process is on-going.

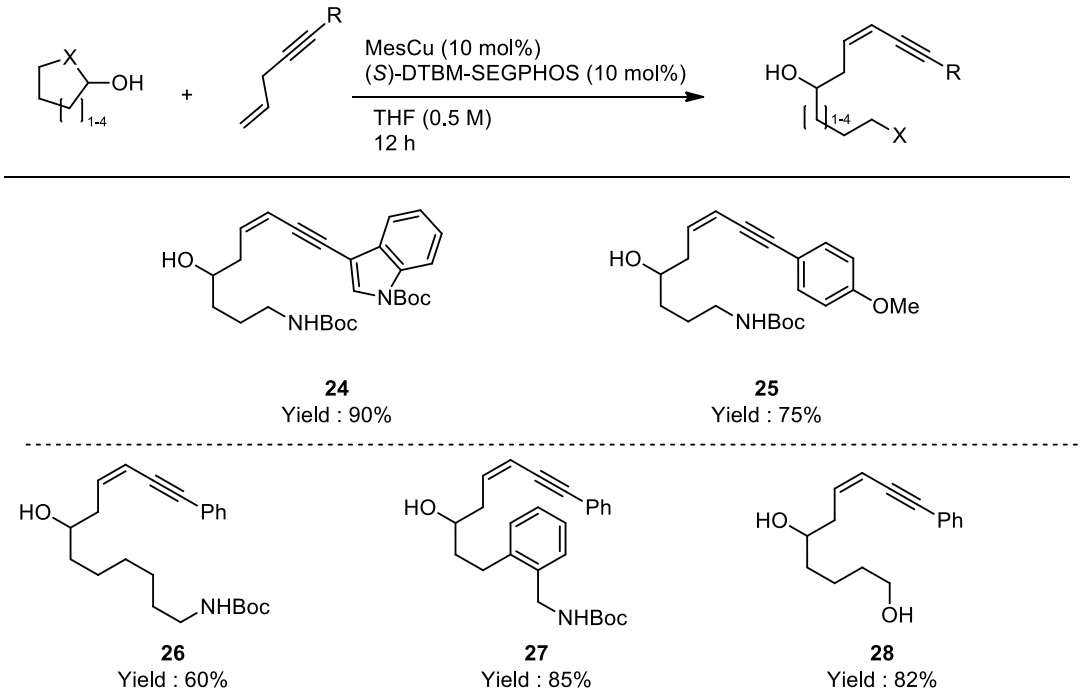
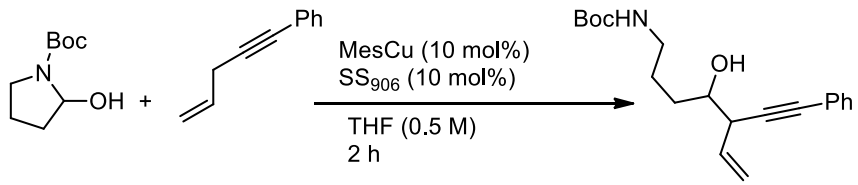


Figure 3.2.2. Substrate scope using (*S*)-DTBM-SEGPHOS as ligand.



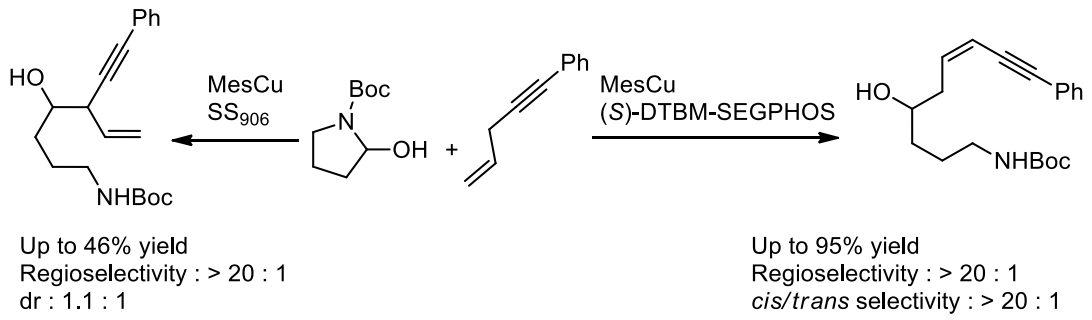
Entry	CF_3CH_2OH	Catalyst	Yield (%)	*dr* (ee~0%)
1[a]	-	MesCu	46	1.1 : 1
2	1 eq.	MesCu	40	2.5 : 1
3[b]	1 eq.	MesCu	15	4.2 : 1
4	1 eq.	$CuClO_4 \bullet 4CH_3CN$ + Barton's base	36	2.8 : 1
5	-	$CuClO_4 \bullet 4CH_3CN$ + proton sponge	18	1.4 : 1
6	2 eq.	MesCu	14	4.5 : 1

a. Reaction time was 12 h. b. Reaction time was 45 mins.

Figure 3.2.3. Optimization of reaction condition for internal product.

3.3 Summary

I have developed the first C-C bond forming reaction via π-activation in the ebsence of electron-withdrawing-group under proton transfer condition. Using the bulky phosphine ligand (*S*)-DTBM-SEGPHOS, the terminal addition was major, the product was obtained in high yield with excellent regio- and cis/trans selectivity, while using the novel bidentate ligand with exceptional large bite angle, the internal product was major. The mild reaction condition enabled high functional group tolerance. The reaction proceeded even in the presence of a hydroxyl group.



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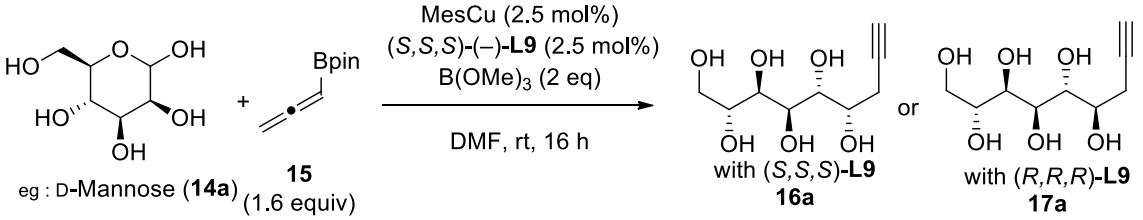
5. Experimental Section

1. An expeditious synthesis of sialic acid derivative by copper(I) - catalyzed stereodivergent propargylation of unprotected aldoses

1.1 General Information

NMR spectra were recorded on JEOL JNM-LA500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), JEOL ECX500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), and JEOL ECX400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR), CHD_2OD (δ = 3.31 for ^{1}H NMR and δ = 49.0 for ^{13}C NMR), or HDO (δ = 4.79 for ^{1}H NMR) as an internal reference. Infrared spectra (IR) were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. ESI-mass spectra were measured on a Waters ZQ4000 spectrometer (for LRMS) and a JEOL JMS-T100LC AccuTOF spectrometer (for HRMS). Preparative HPLC were conducted by using a JASCO HPLC system equipped with a UV-2075 spectrometer, PU-2086 pumps, a DG-2080-53 degasser, and an MX-2080-32 mixer. Reactions were carried out in dry solvents under argon atmosphere, unless otherwise stated. Reagents were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), or Wako Pure Chemical Industries, Ltd., and used after purification by distillation or used without purification for solid substrates. Water for the HPLC analysis was purified using a Millipore MilliQ water purification system.

1.2 Copper-Catalyzed Stereodivergent Propargylation of Aldoses



1.2.1 General procedure for the stereodivergent propargylation of aldoses (Condition A)

A flame-dried 20-mL test tube was charged with mesitylcopper (0.5 mg, 0.0027 mmol), (*S*,*S*,*S*)-Ph-SKP (1.7 mg, 0.0026 mmol), and D-mannose **14a** (18 mg, 0.10 mmol) under argon atmosphere. $B(OMe)_3$ (22 μL, 0.20 mmol) and dry DMF (125 μL) were then added to this mixture. The mixture was stirred for 10 min at room temperature. Allenylboronate **15** (29 μL, 0.16 mmol) was added. After stirring for 16 h at room temperature, the reaction was quenched by the addition of MeOH and concentrated *in vacuo*. The process of MeOH addition followed by evaporation was repeated two-times to give a crude product. The diastereoselectivity was determined by ^{1}H NMR analysis. Products were purified by preparative reverse phase HPLC using a gradient of acetonitrile versus 0.1% TFA in water, affording **16a** as a white solid (19.8 mg, 90% yield). Preparative HPLC was carried out as follows: YMC-Triart C18 (20 mm I.D. × 250 mm) column using a linear gradient of 0-50% acetonitrile in 0.1% aqueous TFA over 30 min at room temperature with a flow rate of 7.0 mL min^{-1}.

The configurations of **16a** and **16g** were determined after converting to KDN (**19a**) and Neu5Ac (**19g**), respectively. The NMR data of synthesized KDN (**19a**) and Neu5Ac (**19g**) were identical to the reported ones (KDN: Nakamura, M.; Furuhata, K.; Yamasaki, T.; Ogura, H. *Chem. Pharm. Bull.* **1991**, *39* 3140., Neu5Ac: Lorpitthaya, R.; Suryawanshi, S. B.; Wang, S.; Pasunooti, K. K.; Cai, S.; Ma, J.; Liu, X.-W. *Angew. Chem. Int. Ed.* **2011**, *50*, 12054). The configurations of other products were tentatively assigned accordingly.

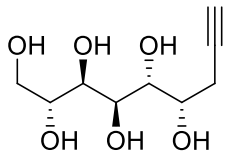
1.2.2 General procedure for the stereodivergent propargylation of 2-deoxy aldoses (Condition B)

A flame-dried 20-mL test tube was charged with $CuClO_4(MeCN)_4$ (0.8 mg, 0.0025 mmol), (*S*,*S*,*S*)-Ph-SKP (1.7 mg, 0.0026 mmol), CF_3COOK (0.8 mg, 0.0053 mmol), MS 3A 40 mg and 2-deoxy-D-ribose (**14h**: 13.4 mg, 0.10 mmol) under argon atmosphere. $B(OMe)_3$ (22 μL, 0.20 mmol) and dry DMF (125 μL) were then added to this mixture. The mixture was stirred at room temperature for 10 min. Allenylboronate **15** (58 μL, 0.32 mmol) was added. After stirring for 16 h at room temperature, the reaction was quenched by the addition of MeOH and concentrated in *vacuo*. The process of MeOH addition followed by evaporation was repeated two-times to give a crude product. The diastereoselectivity was determined by ^1H NMR analysis. Products were purified by preparative reverse phase HPLC using a gradient of acetonitrile versus 0.1% TFA in water, affording **16h** as a white solid (11.3 mg, 65% yield). Preparative HPLC was carried out as follows: YMC-Triart C18 (20 mm I.D ×250 mm) column using a linear gradient of 0-50% acetonitrile in 0.1% aqueous TFA over 30 min at room temperature with a flow rate of 7.0 mL min^{-1}.

1.2.3 Gram-scale synthetic procedure for the stereodivergent propargylation of D-mannose

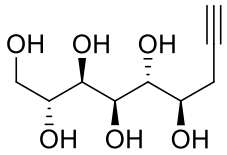
A flame-dried 20-mL bottle was charged with mesitylcopper (3.7 mg, 0.02 mmol), (*S*,*S*,*S*)-Ph-SKP (13.2 mg, 0.02 mmol), and D-Mannose **14a** (1.8 g, 10 mmol) under argon atmosphere. $B(OMe)_3$ (2.2 mL, 20 mmol) and dry DMF (6.3 mL) were then added to this mixture. The mixture was stirred for 10 min at room temperature. Allenylboronate **15** (2.7 mL, 15 mmol) was added. After stirring for 16 h at room temperature, the reaction was quenched by the addition of MeOH and concentrated *in vacuo*. Addition of MeOH-concentration process was repeated two-times to give a crude product. The crude solid was washed successively with EtOAc and MeOH to provide **16a** as a white solid (1.91 g, 87% yield).

1.3 Characterization of propargylation products



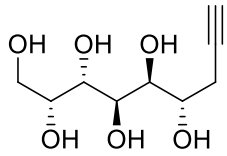
(2*R*,3*R*,4*R*,5*R*,6*S*)-non-8-yne-1,2,3,4,5,6-hexaol (16a)

A white solid, Yield: 90%. ^{1}H NMR (500 MHz, D_2O) δ 3.99 (t, *J* = 6.9 Hz, 1H), 3.79 (d, *J* = 9.6 Hz, 1H), 3.77-3.74 (m, 1H), 3.70 (d, *J* = 8.7 Hz, 1H), 3.67-3.63 (m, 1H), 3.60 (d, *J* = 9.6 Hz, 1H), 3.58-3.53 (m, 1H), 2.47-2.36 (m, 2H), 2.28 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 82.8, 71.8, 71.6, 70.1, 69.7, 68.5, 63.9, 23.6; IR (KBr): 3365, 3231, 1445, 1306, 1094, 1028, 849, 729 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_6$ $[M+Na]^+$ 243.0840 Found 243.0842; $[\alpha]_D^{23.2}$ = +0.2 (*c* = 0.53, H_2O).



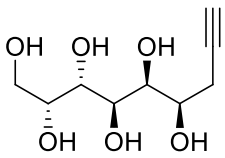
(2*R*,3*R*,4*R*,5*R*,6*R*)-non-8-yne-1,2,3,4,5,6-hexaol (17a)

A white solid, Yield: 81%. ^{1}H NMR (500 MHz, D_2O) δ 3.88 (dt, *J* = 8.6, 4.6 Hz, 1H), 3.74-3.57 (m, 5H), 3.50 (dd, *J* = 11.7, 6.0 Hz, 1H), 2.42 (dt, *J* = 17.2, 3.5 Hz, 1H), 2.34 (ddd, *J* = 17.2, 8.0, 2.6 Hz, 1H), 2.22 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 82.7, 72.8, 71.5, 71.4, 71.2, 70.5, 70.2, 63.9, 21.7; IR (KBr): 3375, 2962, 2896, 1423, 1392, 1088, 1035, 752, 634 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_6$ $[M+Na]^+$ 243.0840 Found 243.0835; $[\alpha]_D^{22.2}$ = +6.4 (*c* = 0.50, H_2O).



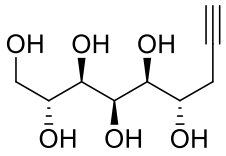
(2*R*,3*S*,4*R*,5*S*,6*S*)-non-8-yne-1,2,3,4,5,6-hexaol (16b)

A white solid, Yield: 73%. ^{1}H NMR (500 MHz, D_2O) δ 3.83 (t, *J* = 6.5 Hz, 1H), 3.77 (d, *J* = 9.5 Hz, 1H), 3.75-3.69 (m, 2H), 3.53 (d, *J* = 6.3 Hz, 2H), 3.51 (d, *J* = 10.3 Hz, 1H), 2.52 (dt, *J* = 17.4, 2.5 Hz, 1H), 2.37 (ddd, *J* = 17.4, 5.4, 2.5 Hz, 1H), 2.22 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 75.1, 72.0, 71.3, 69.7, 68.0, 64.9, 40.9, 28.7; IR (KBr): 3297, 1422, 1112, 1086, 1033 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_6$ $[M+Na]^+$ 243.0840 Found 243.0842; $[\alpha]_D^{22.4}$ = +4.4 (*c* = 0.50, H_2O).



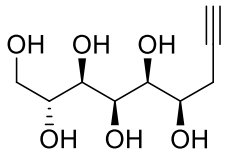
(2*R*,3*S*,4*R*,5*S*,6*R*)-non-8-yne-1,2,3,4,5,6-hexaol (17b)

A white solid, Yield: 66%. ^{1}H NMR (500 MHz, D_2O) δ 3.80-3.73 (m, 3H), 3.60 (d, *J* = 9.2 Hz, 1H), 3.54-3.49 (m, 3H), 2.44-2.40 (m, 1H), 2.34-2.28 (m, 1H), 2.22 (brs, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 81.9, 73.6, 73.2, 71.7, 71.4, 71.2, 64.9, 24.3; IR (KBr): 3398, 2925, 1433, 1103, 1055, 680 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_6$ $[M+Na]^+$ 243.0840 Found 243.0832; $[\alpha]_D^{22.1}$ = +6.1 (*c* = 0.35, H_2O).



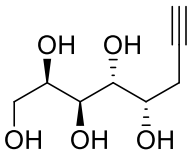
(2*R*,3*R*,4*R*,5*S*,6*S*)-non-8-yne-1,2,3,4,5,6-hexaol (16c)

A white solid, Yield: 76%. ^{1}H NMR (500 MHz, D_2O) δ 3.86 (t, *J* = 2.9 Hz, 1H), 3.74-3.70 (m, 1H), 3.66-3.57 (m, 4H), 3.49 (dd, *J* = 11.4, 5.9 Hz, 1H), 2.45 (dt, *J* = 17.3, 3.4 Hz, 1H), 2.36 (ddd, *J* = 17.3, 6.3, 2.3 Hz, 1H), 2.21 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 81.9, 74.6, 73.6, 71.8, 71.7, 69.2, 68.8, 63.1, 23.0; IR (KBr): 3280, 2918, 1427, 1096, 1028, 667 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_6$ $[M+Na]^+$ 243.0840 Found 243.0835; $[\alpha]_D^{22.9}$ = +2.0 (*c* = 0.51, H_2O).



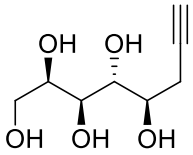
(2*R*,3*R*,4*R*,5*S*,6*R*)-non-8-yne-1,2,3,4,5,6-hexaol (17c)

A white solid, Yield: 72%. (inseparable mixture of **3c** and **4c**) For **4c**: ^{1}H NMR (500 MHz, D_2O) δ 3.95 (dd, *J* = 5.7, 1.7 Hz, 1H), 3.89 (td, *J* = 6.9, 2.9 Hz, 1H), 3.80-3.60 (m, 5H), 2.52 (dd, *J* = 6.9, 2.9 Hz, 1H), 2.27 (t, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 82.0, 74.7, 73.9, 71.8, 71.7, 70.6, 70.0, 63.5, 23.7; IR (KBr): 3387, 2925, 1675, 1204, 1076 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_6$ $[M+Na]^+$ 243.0840 Found 243.0832.



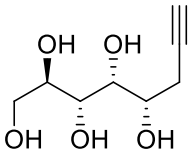
(2*R*,3*S*,4*R*,5*S*)-oct-7-yne-1,2,3,4,5-pentaol (16d)

A white solid, Yield: 84%. ^{1}H NMR (500 MHz, D_2O) δ 4.00 (t, *J* = 7.1 Hz, 1H), 4.89 (t, *J* = 6.4 Hz, 1H), 3.65-3.56 (m, 4H), 2.47 (ddd, *J* = 16.9, 7.5, 2.6 Hz, 1H), 2.40 (ddd, *J* = 16.9, 6.7, 2.6 Hz, 1H), 2.32 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 82.6, 71.6, 71.2, 71.0, 70.2, 69.1, 63.9, 23.7; IR (KBr): 3388, 3217, 1452, 1389, 1294, 1231, 1105, 1052, 735, 657 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$ 213.0734 Found 213.0737; $[\alpha]_D^{22.8}$ = +4.3 (*c* = 0.15, MeOH).



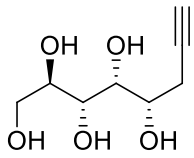
(2*R*,3*S*,4*R*,5*R*)-oct-7-yne-1,2,3,4,5-pentaol (17d)

A white solid, Yield: 81%. ^{1}H NMR (500 MHz, D_2O) δ 3.87 (dt, *J* = 8.6, 4.5 Hz, 1H), 3.80-3.77 (m, 1H), 3.66 (dd, *J* = 8.1, 5.1 Hz, 1H), 3.53-3.48 (m, 3H), 2.41 (dt, *J* = 17.2, 2.9 Hz, 1H), 2.33 (ddd, *J* = 17.2, 7.9, 2.9 Hz, 1H), 2.21 (t, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 82.6, 72.9, 71.6, 71.5, 71.2, 71.0, 63.7, 21.8; IR (KBr): 3326, 2952, 2900, 1458, 1411, 1222, 1095, 1048, 1030, 860, 695, 654 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$ 213.0734 Found 213.0731 ; $[\alpha]_D^{20.8}$ = +9.4 (*c* = 0.86, H_2O).



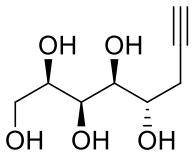
(2*R*,3*S*,4*R*,5*S*)-oct-7-yne-1,2,3,4,5-pentaol (16e)

A white solid, Yield: 95%.^{1}H NMR (500 MHz, D_2O) δ 3.76 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.71 (dd, *J* = 6.2, 2.0 Hz, 1H), 3.67 (dd, *J* = 11.8, 2.9 Hz, 1H), 3.63-3.60 (m, 1H), 3.51-3.47 (m, 2H), 2.40 (ddd, *J* = 17.4, 4.8, 2.3 Hz, 1H), 2.30 (ddd, *J* = 17.4, 6.4, 2.3 Hz, 1H), 2.22 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 81.7, 72.0, 71.9, 71.8, 71.7, 71.2, 63.5, 23.4; IR (KBr): 3430, 3285, 1434, 1089, 1042cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$ 213.0734 Found 213.0737 ; $[\alpha]_D^{21.5}$ = -0.4 (*c* = 0.52, H_2O).



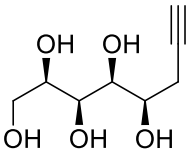
(2*R*,3*S*,4*R*,5*R*)-oct-7-yne-1,2,3,4,5-pentaol (17e)

A white solid, Yield: 93%. ^{1}H NMR (500 MHz, D_2O) δ 3.72-3.64 (m, 4H), 3.60 (ddd, *J* = 8.8, 6.3, 2.8 Hz, 1H), 3.51 (dd, *J* = 11.9, 6.3 Hz, 1H), 2.51 (dt, *J* = 17.3, 2.6 Hz, 1H), 2.37 (ddd, *J* = 17.3, 5.6, 2.6 Hz, 1H), 2.22 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 82.2, 71.9, 71.9, 71.5, 69.8, 68.9, 63.9, 23.9; IR (KBr): 3305, 2949, 1286, 1082, 1041, 644 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$ 213.0734 Found 213.0737; $[\alpha]_D^{22.7}$ = -4.8 (*c* = 0.48, H_2O).



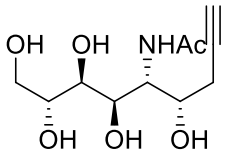
(2*R*,3*S*,4*S*,5*S*)-oct-7-yne-1,2,3,4,5-pentaol (16f)

A white solid, Yield: 65%. ^{1}H NMR (400 MHz, D_2O) δ 3.75-3.64 (m, 3H), 3.60-3.57 (m, 1H), 3.52-3.43 (m, 2H), 2.49 (dt, *J* = 17.3, 2.3 Hz, 1H), 2.36 (ddd, *J* = 17.3, 6.0, 2.3 Hz, 1H), 2.22 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 82.0, 73.7, 73.0, 72.0, 70.2, 69.0, 63.0, 23.4; IR (KBr): 3389, 2934, 1421, 1067, 657 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$ 213.0734 Found 213.0741; $[\alpha]_D^{22.6}$ = +6.4 (*c* = 0.91, H_2O).



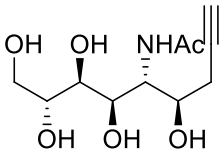
(2*R*,3*S*,4*S*,5*R*)-oct-7-yne-1,2,3,4,5-pentaol (17f)

A white solid, Yield: 60%.^{1}H NMR (500 MHz, D_2O) δ 3.81-3.79 (m, 1H), 3.70-3.67 (m, 1H), 3.61-3.55 (m, 3H), 3.51-3.47 (dd, *J* = 11.5, 6.9 Hz, 1H), 2.41-2.32 (m, 2H), 2.24 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 81.9, 73.2, 72.5, 71.9, 71.8, 70.4, 63.4, 23.5; IR (KBr): 3388, 1420, 1067, 669 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$ 213.0727 Found 213.0734; $[\alpha]_D^{22.8}$ = +2.9 (*c* = 0.68, H_2O).



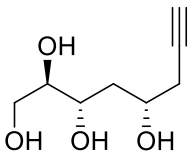
N-((4*S*,5*R*,6*R*,7*S*,8*R*)-4,6,7,8,9-pentahydroxynon-1-yn-5-yl)acetamide (16g)

A white solid, Yield: 70%. ^{1}H NMR (500 MHz, D_2O) δ 4.13 (t, *J* = 6.9 Hz, 1H), 3.94 (d, *J* = 10.4 Hz, 1H), 3.78 (d, *J* = 10.4 Hz, 1H), 3.68 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.61-3.57 (m, 1H), 3.47 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.31 (d, *J* = 9.2 Hz, 1H), 2.26-2.22 (m, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.8, 81.8, 72.4, 71.4, 71.2, 69.7, 68.7, 65.2, 54.7, 25.3, 22.6; IR (KBr): 3499, 3362, 1623, 1541, 1074 cm^{-1}; HRMS (ESI): m/z calcd for $C_{11}H_{19}NO_6$ $[M+Na]^+$ 284.1105 Found 284.1106; $[\alpha]_D^{22.8}$ = -28.9 (*c* = 0.67, H_2O).



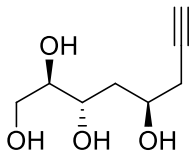
N-((4*R*,5*R*,6*R*,7*S*,8*R*)-4,6,7,8,9-pentahydroxynon-1-yn-5-yl)acetamid (17g)

A white solid, Yield: 51%. ^{1}H NMR (500 MHz, D_2O) δ 4.10 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.98 (ddd, *J* = 7.7, 5.7, 4.3 Hz, 1H), 3.84-3.82 (m, 1H), 3.67 (dd, *J* = 11.9, 2.8 Hz, 1H), 3.57 (ddd, *J* = 9.1, 6.3, 2.8 Hz, 1H), 3.46 (dd, *J* = 11.9, 6.3 Hz, 1H), 3.38 (dd, *J* = 9.1, 0.8 Hz, 1H), 2.41 (ddd, *J* = 17.0, 4.1, 2.6 Hz, 1H), 2.30 (ddd, *J* = 17.0, 7.7, 2.6 Hz, 1H), 2.24 (t, *J* = 2.6 Hz, 1H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.9, 82.1, 71.7, 71.1, 70.2, 69.4, 63.7, 54.3, 22.7, 22.6; IR (neat): 3293, 1639, 1547, 1424, 1378, 1203, 1078, 1031 cm^{-1}; HRMS (ESI): m/z calcd for $C_{11}H_{19}NO_6$ $[M+Na]^+$ 284.1105 Found 284.1118; $[\alpha]_D^{23.3}$ = -4.4 (*c* = 0.84, MeOH).



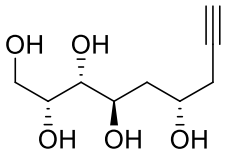
(2*R*,3*S*,5*S*)-oct-7-yne-1,2,3,5-tetraol (16h)

A white solid, Yield: 65%. ^{1}H NMR (500 MHz, CD_3OD) δ 3.97 (dq, *J* = 8.1, 5.7 Hz, 1H), 3.74-3.67 (m, 2H), 3.56 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.46 (dt, *J* = 6.3, 2.9 Hz, 1H), 2.41-2.30 (m, 2H), 2.28 (t, *J* = 2.9 Hz, 1H), 1.99 (ddd, *J* = 14.3, 4.6, 2.9 Hz, 1H), 1.66-1.60 (dt, *J* = 14.3, 9.2 H, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 81.7, 76.3, 72.4, 71.4, 70.0, 64.4, 39.5, 27.8; IR (KBr): 3376, 2923, 1677, 1424, 1204, 1071, 651 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_4$ $[M+Na]^+$ 197.0785 Found 197.0781; $[\alpha]_D^{22.9}$ = -1.6 (*c* = 0.57, MeOH).



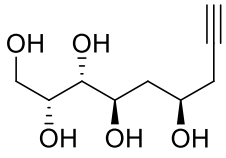
(2*R*,3*S*,5*R*)-oct-7-yne-1,2,3,5-tetraol (17h)

A white solid, Yield: 53%. ^{1}H NMR (500 MHz, CD_3OD) δ 3.98 (dddd, *J* = 9.2, 6.3, 2.9 Hz, 1H), 3.786 (ddd, *J* = 9.8, 6.3, 2.4 Hz, 1H), 3.71 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.56 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.48 (dt, *J* = 6.6, 3.9 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.27 (t, *J* = 2.8 Hz, 1H), 1.77 (ddd, *J* = 14.4, 9.8, 2.7 Hz, 1H), 1.69 (ddd, *J* = 14.4, 9.8, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 81.9, 76.6, 71.3, 70.2, 67.8, 64.7, 40.2, 28.7; IR (KBr): 3375, 2921, 1420, 1064, 652 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_4$ $[M+Na]^+$ 197.0785 Found 197.0781; $[\alpha]_D^{20.6}$ = -28.2 (*c* = 0.64, H_2O).



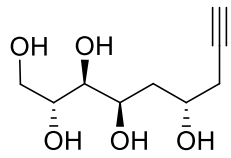
(2*R*,3*R*,4*R*,6*S*)-non-8-yne-1,2,3,4,6-pentaol (16i)

A white solid, Yield: 74%. ^{1}H NMR (500 MHz, CD_3OD) δ 4.03-3.97 (m, 1H), 3.87 (ddd, *J* = 7.6, 6.7, 2.2 Hz, 2H), 3.64-3.58 (m, 2H), 3.36 (dd, *J* = 7.6, 2.2 Hz, 1H), 2.41-2.31 (m, 2H), 2.27 (t, *J* = 2.7 Hz, 1H), 1.88 (ddd, *J* = 14.3, 9.8, 2.4 Hz, 1H), 1.69 (ddd, *J* = 14.3, 9.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 82.5, 74.4, 71.9, 71.2, 68.3, 66.8, 63.7, 39.2, 27.6; IR (KBr): 3280, 3192, 2952, 1466, 1422, 1065, 1030, 707 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_5$ $[M+Na]^+$ 227.0890 Found 227.0887; $[\alpha]_D^{22.8}$ = +23.8 (*c* = 0.49, H_2O).



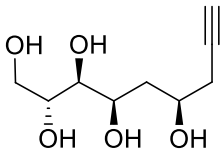
(2*R*,3*R*,4*R*,6*R*)-non-8-yne-1,2,3,4,6-pentaol (17i)

A white solid, Yield: 67%. ^{1}H NMR (500 MHz, CD_3OD) δ 4.00 (dq, *J* = 8.0, 5.6 Hz, 1H), 3.87-3.81 (m, 2H), 3.61 (d, *J* = 6.6 Hz, 2H), 3.37 (dd, *J* = 7.5, 2.1 Hz, 1H), 2.42-2.31 (m, 2H), 2.28 (t, *J* = 2.6 Hz, 1H), 2.02 (ddd, *J* = 14.2, 4.7, 3.0 Hz, 1H), 1.55 (ddd, *J* = 14.2, 9.1, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 81.7,84.6.9, 71.8, 71.7, 70.1, 64.8, 40.2, 27.9; IR (neat): 3375, 1422, 1069 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_5$ $[M+Na]^+$ 227.0890 Found 227.0882, $[\alpha]_D^{21.5}$ = +9.4 (*c* = 0.53, H_2O).



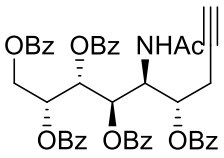
(2*R*,3*S*,4*R*,6*S*)-non-8-yne-1,2,3,4,6-pentaol (16j)

A white solid, Yield: 59%. ^{1}H NMR (400 MHz, CD_3OD) δ 4.13-4.09 (m, 1H), 4.00-3.91 (m, 1H), 3.78 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.67 (ddd, *J* = 8.0, 5.9, 3.5 Hz, 1H), 3.60 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.33 (s, 1H), 2.36 (dd, *J* = 6.2, 2.7 Hz, 2H), 2.26 (t, *J* = 2.7 Hz, 1H), 1.94 (ddd, *J* = 14.3, 10.4, 2.6 Hz, 1H), 1.53 (ddd, *J* = 14.3, 9.8, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 82.0, 75.5, 73.2, 71.3, 68.3, 68.0, 65.1, 41.2, 28.6; IR (neat): 3290, 1420, 1092, 1074, 1025 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_5$ $[M+Na]^+$ 227.0890 Found 227.0900; $[\alpha]_D^{23.8}$ = +31.9 (*c* = 0.28, MeOH).



(2*R*,3*S*,4*R*,6*R*)-non-8-yne-1,2,3,4,6-pentaol (17j)

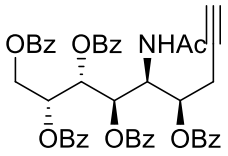
A white solid, Yield: 52%. ^{1}H NMR (500 MHz, CD_3OD) δ 4.06 (dt, *J* = 7.4, 1.8 Hz, 1H), 3.94 (dq, *J* = 11.0, 5.8 Hz, 1H), 3.78 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.67 (ddd, *J* = 8.1, 6.0, 3.5 Hz, 1H), 3.60 (dd, *J* = 8.1, 5.7 Hz, 1H), 3.36 (dd, *J* = 10.4, 5.2 Hz, 1H), 2.42-2.33 (m, 2H), 2.28 (t, *J* = 2.6 Hz, 1H), 1.85-1.82 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 81.7, 74.5, 73.0, 71.4, 69.9, 69.5, 65.1, 40.3, 27.9; IR (KBr): 3280, 2918, 1432, 1089, 1033, 638 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{16}O_5$ $[M+Na]^+$ 227.0890 Found 227.0900; $[\alpha]_D^{22.4}$ = +6.5 (*c* = 0.26, H_2O).



(2*R*,3*R*,4*R*,5*S*,6*S*)-5-acetamidonon-8-yne-1,2,3,4,6-pentayl pentabenzoate (16k-Bz)

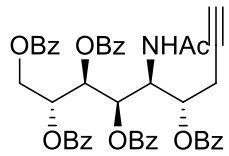
A white solid, Yield: 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.09 (m, 2H), 7.95-7.93 (m, 2H), 7.86-7.84 (m, 4H), 7.70-7.69 (m, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.50-7.43 (m, 5H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.33-7.26 (m, 7H), 7.10 (t, *J* = 7.5 Hz, 2H), 6.12 (d, *J* = 6.9 Hz, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 5.86 (dd, *J* = 7.3, 2.0 Hz, 2H), 5.20 (dd, *J* = 13.0, 6.3 Hz, 1H), 5.11 (dd, *J* = 8.2, 6.3 Hz, 1H), 4.67 (dd, *J* = 11.9, 4.4 Hz, 1H), 4.48 (dd, *J* = 11.9, 6.9 Hz, 1H), 2.75 (ddd, *J* = 17.0, 7.1, 2.6 Hz, 1H), 2.68 (ddd, *J* = 17.0, 6.0, 2.6 Hz, 1H), 2.01 (s, 3H), 1.93 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d6) δ170.4, 166.3, 166.1, 165.9, 165.8, 134.3, 134.2, 134.0, 133.9, 133.7, 131.0, 130.9, 130.9, 130.8, 130.7, 130.6, 130.5, 130.3, 130.2, 129.4,

129.3, 129.2, 129.1, 129.0, 79.8, 72.5, 72.0, 71.9, 71.0, 70.4, 69.5, 64.3, 50.5, 50.4, 22.9, 21.9; IR (neat): 3390, 1721, 1683, 1259, 1092, 1067, 708 cm^{-1}; HRMS (ESI): m/z calcd for $C_{46}H_{39}NO_{11}$ $[M+Na]^+$ 804.2416 Found 804.2399; $[\alpha]_D^{22.9}$ = -13.9 (*c* = 0.65, MeOH).



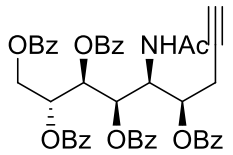
(2*R*,3*R*,4*R*,5*S*,6*R*)-5-acetamidonon-8-yne-1,2,3,4,6-pentayl pentabenzoate (17k-Bz)

A white solid, Yield: 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.4 Hz, 2H), 7.95 (d, *J* = 7.4 Hz, 2H), 7.86-7.80 (m, 6H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 13.1, 7.4 Hz, 2H), 7.42 (dd, *J* = 10.8, 4.4 Hz, 4H), 7.32-7.24 (m, 8H), 5.93-5.89 (m, 4H), 5.26 (dd, *J* = 11.3, 5.6 Hz, 1H), 5.16 (dd, *J* = 9.8, 6.3 Hz, 1H), 4.73 (dd, *J* = 11.9, 4.3 Hz, 1H), 4.48 (dd, *J* = 11.9, 7.4 Hz, 1H), 2.75 (ddd, *J* = 17.3, 5.0, 2.6 Hz, 1H), 2.64 (ddd, *J* = 17.3, 5.7, 2.6 Hz, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, acetone-d6) δ170.9, 166.3, 166.1, 166.0, 165.9, 134.2, 134.1, 134.0, 133.9, 133.8, 130.9, 130.8, 130.6, 130.5, 130.4, 130.3, 130.2, 130.1, 129.3, 129.2, 129.1, 129.0, 79.6, 73.2, 72.8, 71.4, 70.9, 70.2, 64.5, 50.4, 22.8, 22.3; IR (neat): 3376, 1719, 1683, 1246, 1092, 1067, 708 cm^{-1}; HRMS (ESI): m/z calcd for $C_{46}H_{39}NO_{11}$ $[M+Na]^+$ 804.2416 Found 804.2399; $[\alpha]_D^{22.8}$ = -17.4 (*c* = 0.45, MeOH).



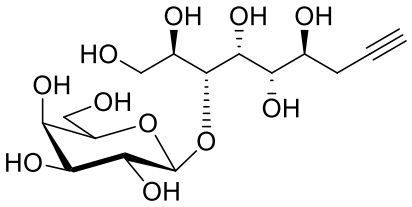
(2*R*,3*S*,4*R*,5*S*,6*S*)-5-acetamidonon-8-yne-1,2,3,4,6-pentayl pentabenzoate (16l-Bz)

A white solid, Yield: 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-7.99 (m, 4H), 7.847.82 (m, 2H), 7.73 (dd, *J* = 8.1, 7.5 Hz, 4H), 7.54 (dt, *J* = 7.5, 1.0 Hz, 2H), 7.45-7.35 (m, 8H), 7.26-7.17 (m, 5H), 5.99-5.92 (m, 2H), 5.85 (dt, *J* = 5.9, 3.0 Hz, 1H), 5.23 (dd, *J* = 13.2, 6.3 Hz, 1H), 5.16 (dd, *J* = 7.3, 1.8 Hz, 1H), 4.87 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.59 (dd, *J* = 12.3, 5.9 Hz, 1H), 2.72 (ddd, *J* = 17.2, 6.4, 2.7 Hz, 1H), 2.65 (ddd, *J* = 17.2, 5.9, 2.7 Hz, 1H), 2.11 (s, 3H), 1.86 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d6) δ171.1, 166.5, 166.1, 165.8, 165.7, 134.2, 134.1, 134.1, 134.0, 133.9, 130.8, 130.7, 130.6,130.6, 130.6, 130.5, 130.4, 130.4, 130.2, 129.4, 129.4, 129.3, 129.2, 129.2, 129.0, 79.8, 72.4, 72.0, 71.3, 71.2, 70.4, 63.2, , 51.9, 51.8, 23.0, 22.2; IR (neat): 3418, 1717, 1653, 1261, 1093, 709 cm^{-1}; HRMS (ESI): m/z calcd for $C_{46}H_{39}NO_{11}$ $[M+Na]^+$ 804.2416 Found 804.2399; $[\alpha]_D^{22.8}$ = +12.6 (*c* = 0.44, MeOH).



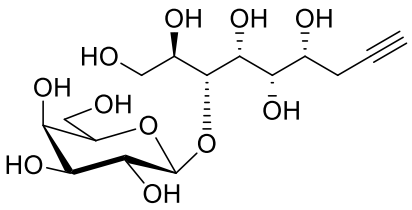
(2*R*,3*S*,4*R*,5*S*,6*R*)-5-acetamidonon-8-yne-1,2,3,4,6-pentayl pentabenzoate (17l-Bz)

A white solid, Yield: 51%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.07 (m, 2H), 8.07-8.03 (m, 2H), 8.03-7.99 (m, 2H), 7.92-7.88 (m, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.58 (dd, *J* = 15.3, 7.5 Hz, 2H), 7.53 (dd, *J* = 13.0, 6.9 Hz, 2H), 7.44-7.33 (m, 10H), 7.19 (t, *J* = 7.7 Hz, 2H), 6.33 (dd, *J* = 8.2, 3.1 Hz, 1H), 5.81-5.72 (m, 4H), 5.01-4.95 (m, 1H), 4.79 (dd, *J* = 12.4, 2.7 Hz, 1H), 4.49 (dd, *J* = 12.4, 5.0 Hz, 1H), 2.67-2.56 (m, 2H), 1.78 (s, 3H), 1.70 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d6) δ 170.9, 166.5, 166.5, 166.4, 166.3, 134.5, 134.2, 134.2, 134.0, 133.9, 130.8, 130.8, 130.7, 130.6, 130.6, 130.5, 130.3, 130.3, 130.2, 129.5, 129.3, 129.2, 129.2, 100.8, 79.7, 72.3, 72.1, 71.8, 70.6, 63.1, 51.5, 22.7, 22.5; IR (neat): 3384, 1711, 1674, 1241, 1090, 1066, 1024, 706 cm^{-1}; HRMS (ESI): m/z calcd for $C_{46}H_{39}NO_{11}$ $[M+Na]^+$ 804.2416 Found 804.2399; $[\alpha]_D^{23.1}$ =+19.8 (*c* = 1.17, MeOH).



(2*R*,3*R*,4*R*,5*S*,6*S*)-3-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)non-8-yne-1,2,4,5,6-pentaol (16m)

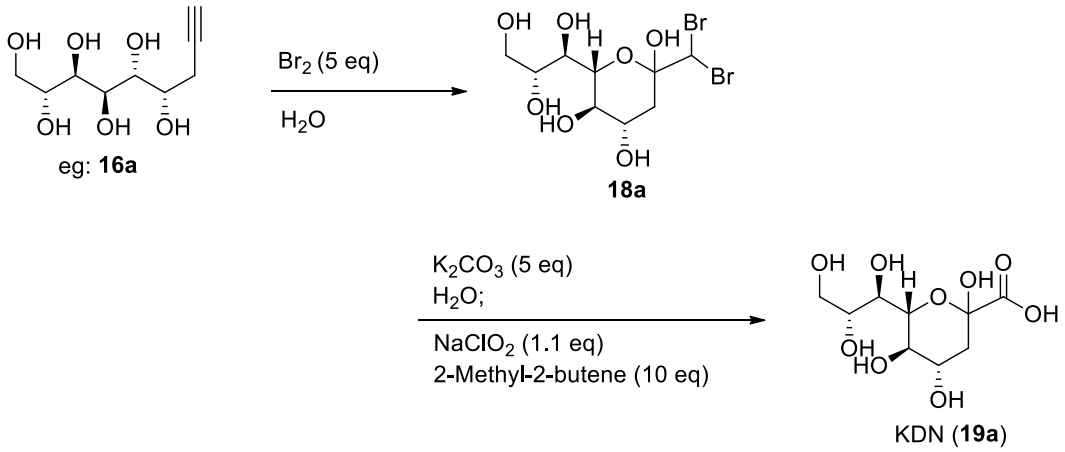
A white solid, Yield: 56%. ^{1}H NMR (500 MHz, D_2O) δ 4.39 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 1H), 3.78-3.38 (m, 12H), 2.45 (dt, *J* = 17.3, 2.5 Hz, 1H), 2.35 (ddd, *J* = 17.3, 6.1, 2.5 Hz, 1H), 2.23 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 104.1, 82.2, 82.1, 75.9, 73.7, 73.2, 72.1, 71.9, 71.8, 69.3, 69.1, 68.9, 62.7, 61.7, 23.1; IR (neat): 3398, 1642, 1424, 1074 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{26}O_{11}$ $[M+Na]^+$ 405.1368 Found 405.1367; $[\alpha]_D^{23.0}$ = +7.4 (*c* = 0.87, H_2O).



(2*R*,3*R*,4*R*,5*S*,6*R*)-3-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)non-8-yne-1,2,4,5,6-pentaol (17m)

A white solid, Yield: 45%. ^{1}H NMR (500 MHz, D_2O) δ 4.34 (d, *J* = 7.5 Hz 1H), 3.90-3.87 (m, 1H), 3.81-3.47 (m, 11H), 3.38-3.35 (m, 1H), 2.38 (ddd, *J* = 9.4, 7.4, 2.5 Hz, 1H), 2.33-2.26 (m, 1H), 2.23 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 103.7, 82.5, 79.8, 75.6, 73.5, 73.2, 71.9, 71.8, 71.7, 70.6, 70.0, 69.2, 62.7, 61.5, 23.8; IR (neat): 3409, 1643, 1423, 1075 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{26}O_{11}$ $[M+Na]^+$ 405.1368 Found 405.1367; $[\alpha]_D^{23.1}$ = +6.7 (*c* = 1.09, H_2O).

1.3 Rapid Synthesis of Sialic Acid Derivatives



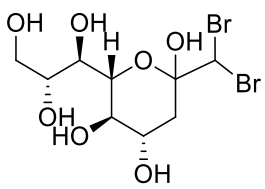
1.3.1 General procedure for sialic acid synthesis

3-Deoxy-D-glycero-β-D-galacto-2-nonulosonic acid (19a)

To a 100 mL round bottom flask containing compound **16a** (1.1 g, 5 mmol) in 22.5 mL H_2O was added Br_2 (2.0 g, 25 mmol). The resulting reaction mixture was stirred for 10 min at room temperature to afford **18a**. Excess amont of bromine was removed *via* extraction with hexane (30 mL, 3 times). The product was used directly into the next step without purification. To a solution of **18a** in H_2O (22.5 mL) was added K_2CO_3 (3.46 g, 25 mmol). The mixture was stirred for 1 h at room temperature until TLC analysis indicated completion of the reaction. Subsequently, CH_3COOH was added to the reaction mixture until pH = 4. To the mixture were added *t*-BuOH (22.5 mL) and

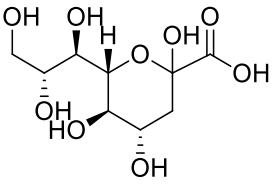
2-methyl-2-butene (5.3 mL, 50 mmol). $NaClO_2$ (497 mg, 5.5 mmol) dissolved in 5 mL water was added dropwise, and the mixture was stirred for 10 min at room temperature. The solution was evaporated, and the resulting crude residue was passed through a Dowex 1X8 resin (formate form) using aqueous formic acid solution (0-1 M) as an eluent. The solvent was removed *via* lyophilisation to afford **19a** as white powder (1.02 g, 76% yield).

1.3.2 Characterization of sialic acids



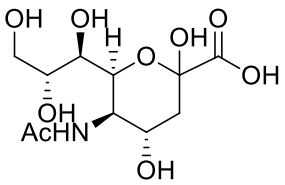
(4*S*,5*R*,6*R*)-2-(dibromomethyl)-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2H-pyran-2,4,5-triol (18a)

^{1}H NMR (500 MHz, D_2O) δ 5.81 (s, 1H), 3.90-3.85 (m, 2H), 3.81 (d, *J* = 9.8 Hz, 2H), 3.70-3.68 (m, 1H), 3.63 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.44 (t, *J* = 9.75 Hz, 1H), 2.42 (dd, *J* = 12.6, 5.2 Hz, 1H) 1.59 (t, *J* = 12.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 97.9, 73.7, 72.3, 71.8, 71.0, 69.9, 65.0, 53.9, 39.5;IR (KBr): 3376, 1655, 1420, 1066, 1034; HRMS (ESI): m/z calcd for $C_9H_{16}Br_2O_7$ $[M+Na]^+$ 418.9135 Found 418.9146; $[\alpha]_D^{23.5}$ = -12.7 (*c* = 0.49, MeOH).



KDN (19a)

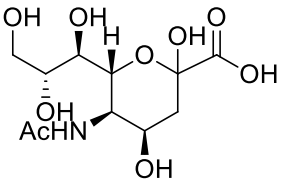
^{1}H NMR (500 MHz, D_2O) δ 3.93-3.88 (m, 2H), 3.79-3.75 (m, 2H), 3.67-3.64 (m, 1H), 3.57 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.49 (t, *J* = 9.8 Hz, 1H), 2.18 (dd, *J* = 13.2, 4.6 Hz, 1H), 1.74 (t, *J* = 13.2 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 173.9, 95.9, 72.4, 71.1, 70.7, 69.3, 68.5, 63.9, 39.2; IR (KBr): 3399, 1743, 1440, 1281, 1210, 691 cm^{-1} HRMS (ESI): m/z calcd for $C_9H_{16}O_9$ $[M-H]^-$ 267.0721 Found 267.0721. $[\alpha]_D^{25}$ = -42 (*c* = 1, H_2O).



Neu5Ac (19g)

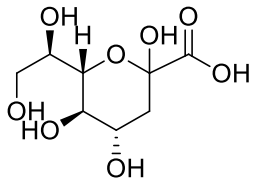
The reaction was conducted by following the general procedure, using **16g** (26.1 mg, 0.1 mmol), Br_2 (40 mg, 0.5 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at room temperature for 5 min. Excess amont of bromine was removed *via* extraction with hexane. The product was used directly into the next step without purification. K_2CO_3 (69.1 mg, 0.5 mmol) was added to the crude product dissolved in H_2O (0.5 mL). The reaction was stirred for 30 min. Then CH_3COOH was added dropwise until pH = 4, and Pinnick oxidation using $NaClO_2$ (9.9 mg, 0.11 mmol), *t*BuOH (0.5 mL) and 2-methyl-2-butene (0.11 mL, 1 mmol) was carried out in one pot. The solution was evaporated, and the resulting crude residue was passed through a Dowex 1X8 resin (formate form) using aqueous formic acid solution (0-1 M) as an eluent. The solvent was removed *via* lyophilisation to afford **19g** as white powder (22.9 mg, 74% yield).

^{1}H NMR (500 MHz, D_2O) δ 3.94-3.86 (m, 2H), 3.77 (t, *J* = 10.2 Hz, 1H), 3.69 (dd, *J* = 11.9, 2.6 Hz, 1H), 3.60 (ddd, *J* = 9.1, 6.4, 2.6 Hz, 1H), 3.46 (dd, *J* = 11.9, 6.4 Hz, 1H), 3.38 (dd, *J* = 9.1, 0.7 Hz, 1H), 2.11 (dd, *J* = 13.0, 4.9 Hz, 1H), 1.89 (s, 3H), 1.70 (dd, *J* = 13.0, 11.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 175.6, 174.0, 96.0, 71.1, 70.9, 68.9, 67.4, 63.9, 52.8, 39.5, 22.8; IR (KBr): 3433, 3398, 1719, 1637, 1559, 1457, 1128, 1069, 1036 cm^{-1} HRMS (ESI): m/z calcd for $C_{11}H_{19}NO_9$ $[M-H]^-$ 308.0987 Found 308.0994, $[\alpha]_D^{23.4}$ = -13.2 (*c* = 0.27, H_2O).



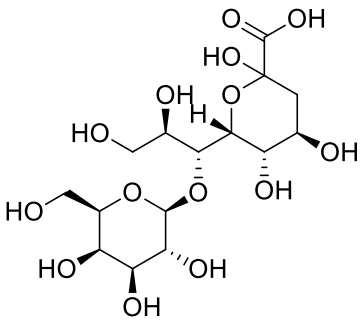
4-*epi*-Neu5Ac (19g')

Using **17g** (26.1 mg, 0.1 mmol), the reaction was conducted by following the procedure for preparing **19g**. The corresponding product was obtained as a pale pink solid (20.1 mg, 65% from **17g**). Mixture of anomers. For the major isomer: ^{1}H NMR (500 MHz, D_2O) δ 4.20 (d, *J* = 10.8 Hz, 1H), 4.05-3.94 (m, 2H), 3.64 (dd, *J* = 11.8, 2.4 Hz, 1H), 3.61 (ddd, *J* = 9.0, 5.6, 2.4 Hz, 1H), 3.50-3.40 (m, 2H), 2.02 (dd, *J* = 14.9, 3.3 Hz, 1H), 1.97 (dd, *J* = 14.9, 3.3 Hz, 1H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 174.9, 174.0, 95.8, 70.7, 69.1, 66.7, 66.4, 63.9, 48.3, 36.8, 22.6; IR (KBr): 3397, 1750, 1735, 1654, 1637, 1628, 1125, 1089, 1031 cm^{-1} HRMS (ESI): m/z calcd for $C_{11}H_{19}NO_9$ $[M-H]^-$ 308.0987 Found 308.0994,



(4*S*,5*R*,6*S*)-6-((*R*)-1,2-dihydroxyethyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid (19d)

Using **16d** (19 mg, 0.1 mmol), the reaction was conducted by following the procedure for preparing **19g**. The corresponding product was obtained as a white solid. (19.5 mg, 82% from **16d**). ^{1}H NMR (500 MHz, D_2O) δ 3.91-3.88 (m, 1H), 3.81 (ddd, *J* = 11.6, 9.2, 5.1 Hz, 1H), 3.62-3.58 (m, 1H), 3.53 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.49-3.41 (m, 2H), 2.07 (dd, *J* = 13.0, 5.1 Hz, 1H), 1.65 (t, *J* = 13.0, 1H); ^{13}C NMR (125 MHz, D_2O) δ 174.5, 96.1, 73.3, 70.8, 69.3, 69.3, 63.5, 39.3; IR (KBr): 3406, 1685, 1438, 1403, 1207, 1142, 624 cm^{-1}; HRMS (ESI): m/z calcd for $C_8H_{14}O_8$ [M-H]$^-$ 237.0615 Found 237.0626; $[\alpha]_D^{22.6}$ = -4.5 (*c* = 6.78, H_2O)



(4*R*,5*S*,6*R*)-6-((1*R*,2*R*)-2,3-dihydroxy-1-(((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)propyl)-2,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid (19m)

The reaction was conducted by following the general procedure, using **17m** (100 mg, 0.26 mmol), KBr (74.8 mg, 0.63 mmol), and Oxone (193 mg, 0.63 mmol) in H_2O (2.4 mL). The reaction mixture was stirred at room temperature for 5 min. Inorganic salts were roughly removed using C_{18} reverse phase column, and the crude product was used directly for the next step without further purification. K_2CO_3 (144 mg, 1.0 mmol) was added to the crude product dissolved in H_2O (2.4 mL). The reaction was stirred for 30 min. Then CH_3COOH was added dropwise until pH = 4, and Pinnick oxidation using $NaClO_2$ (25.9 mg, 0.29 mmol), *t*BuOH (2.4 mL), and 2-methyl-2-butene (275 μL, 0.90 mmol) was carried out in one pot. The crude product was passed through a Dowex 1X8 resin (acetate form) using aqueous CH_3COOH solution (0-2 M) as an eluent. Products were purified by preparative reverse phase HPLC using a gradient of acetonitrile versus 0.1% TFA in water, affording **19m** as a white solid (59.3 mg, 53% from **17m**). Preparative HPLC was carried out as follows: YMC-Triart C18 (20 mm I.D ×250 mm) column using a linear gradient of 0-50% acetonitrile in 0.1% aqueous TFA over 30 min at room temperature with a flow rate of 7.0 mL min^{-1}.

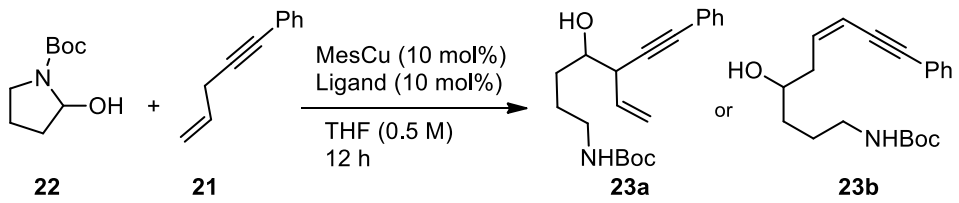
^{1}H NMR (400 MHz, D_2O) δ 4.33 (dd, *J* = 7.7, 2.1 Hz, 1H), 4.17 (dd, *J* = 9.3, 2.1 Hz, 1H), 3.83-3.76 (m, 5H), 3.63-3.48 (m, 6H), 3.40-3.35 (m, 1H), 2.92 (ddd, *J* = 18.1, 5.1, 2.2 Hz, 1H), 2.41 (dd, *J* = 18.1, 2.2 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 180.4, 103.5, 87.1, 76.8, 75.6, 73.2, 71.7, 71.4, 69.3, 68.5, 67.9, 62.8, 61.9, 40.3; IR (neat): 3389, 1758, 1638, 1077, 1043; HRMS (ESI): m/z calcd for $C_{15}H_{26}O_{14}$ $[M-H]^-$ 429.1249 Found 429.1266; $[\alpha]_D^{21.3}$ = +21.5 (*c* = 2.28, H_2O).

2. Ligand-Controlled Copper(I)-Catalyzed Regiodivergent Synthesis of Conjugated and Skipped Ene-ynes

2.1 General Information

NMR spectra were recorded on JEOL JNM-LA500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), JEOL ECX500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), and JEOL ECX400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR), CHD_2OD (δ = 3.31 for ^{1}H NMR and δ = 49.0 for ^{13}C NMR) as an internal reference. Infrared spectra (IR) were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. ESI-mass spectra were measured on a Waters ZQ4000 spectrometer (for LRMS) and a JEOL JMS-T100LC AccuTOF spectrometer (for HRMS). The regioselectivity and cis/trans selectivity were determined by NMR analysis of crude product. The diastereoselectivity was determined by HPLC analysis. HPLC analysis was performed on JASCO HPLC system containing of following : Pump, PU-2080; detector, UV-2075; measured at 254 nm, 210 nm, 220 nm; chiral column : IA, OD-H. Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Reactions were carried out in dry solvents under argon atmosphere, unless otherwise stated. Reagents were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), or Wako Pure Chemical Industries, Ltd., and used after purification by distillation or used without purification for solid substrates.

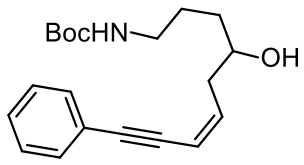
2.2 General procedure



Method A : A flame-dried 20-mL test tube was charged with mesitylcopper (1.8 mg, 0.01 mmol), (*S*)-DTBM-SEGPHOS (12 mg, 0.01 mmol) in 200 µL THF. The solution was stirred for 5 mins. Hemiaminal (18.7 mg, 0.1 mmol) (**22**) and nucleophile (22.8 µL , 0.15 mmol) (**21**) was added sequentially. under argon atmosphere. After stirring for 12 h at room temperature, the crude mixture was purified directly by column chromatography to afford product **23b** in 95% isolated yield with > 20 : 1 regioselectivity and > 20 : 1 *cis/trans* selectivity.

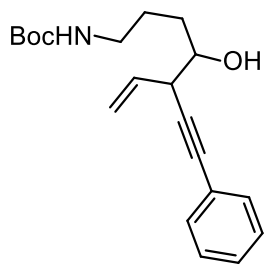
Method B : A flame-dried 20-mL test tube was charged with mesitylcopper (1.8 mg, 0.01 mmol), SS_{906} (9.1 mg, 0.01 mmol) in 200µL THF. The solution was stirred for 5 mins. Hemiaminal (18.7 mg, 0.1 mmol) (**22**) and nucleophile (22.8 µL , 0.15 mmol) (**21**) was added sequentially under argon atmosphere. After stirring for 12 h at room temperature, the crude mixture was purified directly by column chromatography to afford product **23a** in 46% isolated yield with > 20 : 1 regioselectivity and 1.1 : 1 diastereoselectivity.

1.3 Characterization of products



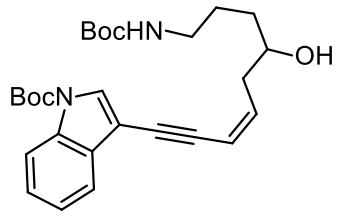
(*Z*)-*tert*-butyl (4-hydroxy-9-phenylnon-6-en-8-yn-1-yl) carbamate (23a)

Colourless oil, Yield: 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.42 (m, 2H), 7.27-7.30 (m, 3H), 6.01-6.06 (m, 1H), 5.81 (d, *J* = 10.9 Hz, 1H), 4.57 (s, 1H), 3.76-3.80 (m, 1H), 3.09-3.15 (m, 2H), 2.55-2.61 (m, 2 H), 1.51-1.63 (m, 4H), 1.41 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$)) δ156.1, 139.2, 131.4, 128.3, 128.2, 123.3, 111.8, 94.6, 85.9, 71.0, 41.6, 40.4, 38.5, 33.8, 28.4, 26.4; Low resolution mass for $[C_{20}H_{27}NO_3+Na]^+$ *m/z* found 352.1; HRMS (ESI): m/z calcd for $[C_{20}H_{27}NO_3+Na]^+$ 352.1883 Found 352.1888.



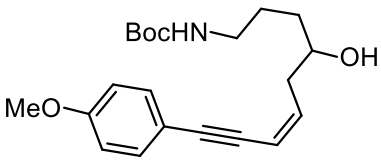
***tert*-butyl (4-hydroxy-5-(phenylethynyl)hept-6-en-1-yl) carbamate (23b)**

White solid, Yield: 46%. (inseparable mixture of diastereoisomers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.27-7.29 (m, 3H), 5.82-5.89 (m, 1H), 5.39-5.49 (m, 1H), 5.26-5.28 (m, 1H), 4.59 (s, 1H), 3.68-3.72 (m, 1H), 3.36-3.41 (m, 1H), 3.13-3.16 (m, 2H), 1.69-1.75 (m, 2H), 1.53-1.61 (m, 2H), 1.40 (s, 9H); Low resolution mass for $[C_{20}H_{27}NO_3+Na]^+$ *m/z* found 352.2; HRMS (ESI): m/z calcd for $[C_{20}H_{27}NO_3+Na]^+$ 352.1883 Found 352.1888.



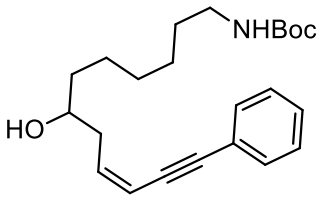
(*Z*)-*tert*-butyl 3-(9-((*tert*-butoxycarbonyl)amino)-6-hydroxynon-3-en-1-yn-1-yl)-1H- indole-1-carboxylate (24)

A yellow solid, Yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 2H), 7.73 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.34 (td, *J* = 1.2 Hz, 7.5 Hz, 1H), 7.28 (td, *J* = 1.2 Hz, 7.5 Hz, 1H), 6.10 (m, 1H), 5.87 (d, *J* = 1.2 Hz, 10.9 Hz, 1H), 4.59 (s, 1 H), 3.80-3.83 (m, 1H), 3.09-3.17 (m, 2H), 2.58-2.64 (m, 2H), 1.60 (s, 9H), 1.49-1.59 (m. 4H), 1.40 (s, 9H) ; ^{13}C NMR (125 MHz, acetone-d6) δ156.1, 149.0, 138.8, 134.6, 130.4, 128.5, 125.2, 123.2, 119.9, 115.2, 111.8, 103.5, 89.4, 85.9, 84.3, 79.1, 70.9, 40.4, 38.5, 33.8, 28.4, 28.1, 26.4; Low resolution mass for $[C_{27}H_{36}N_2O_5+Na]^+$ *m/z* found 491.3; HRMS (ESI): m/z calcd for $[C_{27}H_{36}N_2O_5+Na]^+$ 491.2492 Found 491.2496.



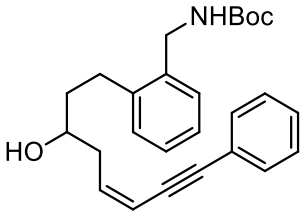
(*Z*)-*tert*-butyl (4-hydroxy-9-(4-methoxyphenyl)non -6-en-8-yn-1-yl)carbamate (25)

Colourless oil, Yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.36 (m, 2H), 6.80-6.83 (m, 3H), 5.95-6.00 (m, 1H), 5.79 (d, *J* = 10.9 Hz, 1H), 4.59 (s, 1H), 3.78-3.79 (m, 4H), 3.08-3.16 (m, 2H), 2.51-2.60 (m, 2H), 1.53-1.58 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, acetone-d6) δ159.6, 156.1, 132.8, 115.4, 113.9, 111.9, 94.1, 84.7, 79.2, 71.0, 55.3, 55.2, 40.4, 38.4, 33.8, 28.4, 26.4; Low resolution mass for $[C_{21}H_{29}NO_4+Na]^+$ *m/z* found 382.2; HRMS (ESI): m/z calcd for $[C_{21}H_{29}NO_4+Na]^+$ 382.1989 Found 382.1995.



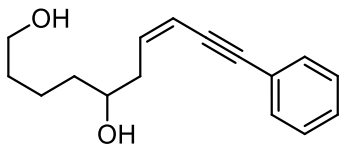
(Z)-*tert*-butyl (7-hydroxy-12-phenyldodec-9-en-11-yn-1-yl) carbamate (26)

Colourless oil, Yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.42 (m, 2H), 7.25-7.30 (m, 3H), 6.01-6.07 (m, 1H), 5.80 (d, *J* = 10.9 Hz, 1H), 4.45 (s, 1H), 3.74-3.77 (m, 1H), 3.04-3.07 (m, 2H), 2.51-2.62 (m, 2H), ; ^{13}C NMR (125 MHz, acetone-d6) δ155.9, 139.5, 131.4, 128.3, 128.1, 123.3, 111.6, 93.9, 86.1, 79.0, 71.3, 40.5, 38.3, 36.9, 29.9, 29.2, 28.4, 26.7, 25.5; Low resolution mass for $[C_{23}H_{33}NO_3+Na]^+$ *m/z* found 394.2; HRMS (ESI): m/z calcd for $[C_{23}H_{33}NO_3+Na]^+$ 394.2353 Found 394.2365.



(*Z*)-tert-butyl 2-(3-hydroxy-8-phenyloct-5-en-7-yn-1-yl) benzylcarbamate (27)

A colourless oil, Yield: 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 2H), 7.73 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.34 (td, *J* = 1.2 Hz, 7.5 Hz, 1H), 7.28 (td, *J* = 1.2 Hz, 7.5 Hz, 1H), 6.10 (m, 1H), 5.87 (d, *J* = 1.2 Hz, 10.9 Hz, 1H), 4.59 (s, 1 H), 3.80-3.83 (m, 1H), 3.09-3.17 (m, 2H), 2.58-2.64 (m, 2H), 1.60 (s, 9H), 1.49-1.59 (m. 4H), 1.40 (s, 9H) ; ^{13}C NMR (125 MHz, acetone-d6) δ155.8, 140.4, 139.4, 136.3, 131.4, 129.7, 128.9, 128.3, 128.1, 127.8, 126.3, 123.3, 111.5, 94.0, 86.1, 79.6, 70.5, 42.2, 41.5, 38.5, 31.9, 28.4 ; Low resolution mass for $[C_{26}H_{31}NO_3+Na]^+$ *m/z* found 428.2; HRMS (ESI): m/z calcd for $[C_{26}H_{31}NO_3+Na]^+$ 428.2196 Found 428.2203.



(*Z*)-10-phenyldec-7-en-9-yne-1,5-diol (28)

Colourless oil, Yield: 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.27-7.32 (m, 3H), 6.01-6.06 (m, 1H), 5.81 (d, *J* = 10.3 Hz, 1H), 3.76-3.81 (m, 1H), 3.63 (t, *J* = 6.3 Hz, 1H), 2.52-2.61 (m, 2H), 1.44-1.58 (m, 6 H) ; ^{13}C NMR (125 MHz, acetone-d6) δ139.4, 131.4, 128.3, 128.2, 123.2, 111.7, 94.0, 86.0, 71.2, 62.7, 38.3, 36.6, 32.5, 21.8; Low resolution mass for $[C_{16}H_{20}O_2+Na]^+$ *m/z* found 267.1; HRMS (ESI): m/z calcd for $[C_{16}H_{20}O_2+Na]^+$ 267.1356 Found 267.1378.

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